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Muscarinic antagonists play an important role in anticholinesterase agent therapy by reducing the response of muscarinic receptors to acetylcholine, acting synergistically with cholinesterase reactivators. Therapy with antagonists such as atropine is difficult to manage because of the toxicity of these compounds; atropine antagonizes the receptor whether or not acetylcholine levels are elevated.

Our approach to the development of a better antidote is to design a molecule whose concentration and resulting muscarinic antagonist activity is controlled by the degree of cholinesterase inhibition, and thus by the need for the drug. This is accomplished by incorporating into the same molecule features that confer muscarinic antagonism and susceptibility to hydrolysis by cholinesterase. Such compounds should be rapidly degraded by cholinesterase to inactive products in a normal system, but should remain active when cholinesterase has been inhibited. As

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the cholinesterase activity recovers, the compounds should again be hydrolyzed. The proper combination of muscarinic antagonism and susceptibility to cholinesterase hydrolysis should allow these compounds to be used at higher doses with fewer side effects.

During this contract we have continued to investigate the structure-activity relationships for esters of S-(-)-tropic acid and (-)-4-chlorotropic acid. A variety of quaternary salts of 2-*N*,*N*-dialkylaminoethyl and 2-(1-piperidinylethyl) esters of both acids have been synthesized and tested ***in vitro*** for muscarinic receptor binding and rates of hydrolysis by serum cholinesterase. The results show that the majority of the compounds tested bind to the muscarinic receptor in rat brain homogenates with an affinity similar to that of atropine and that several of these compounds (e.g. **SR 4952** and **SR 4953**) bind significantly more strongly. Cholinesterase hydrolysis of these compounds proceeded as expected ($t_{1/2}$ = 29-68 min). The derivatives of (-)-4-chlorotropic acid did not bind as strongly to the muscarinic receptor as their S-(-)-tropic acid counterparts and were hydrolyzed more rapidly by cholinesterase.

Several of the compounds have been tested *in vivo* by USAMRICD as either reactivators or pretreatment drugs but unfortunately not as atropine substitutes in the anticholinergic survival efficacy screen. The results in these assays have been rather disappointing as might have been expected. We have therefore been unable to determine whether any of these drugs have any therapeutic value and could have any potential as substitutes for atropine in humans.

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the US Army.

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The synthesis described in this report was performed by Dr. Michael Tracy, Dr. Andrew B. Kelson, and Mr. Kenneth J. Ryan and the *in vitro* pharmacological assays by Dr. Larry R. Toll and Ms Susan R. Brandt.

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INTRODUCTION

This report summarizes the technical efforts undertaken on U.S. Army Medical Research and Development Command Contract No. DAMD17-88-C-8147 and covers progress during the period 1 September 1988 through 31 August 1990.

Poisoning by organophosphorous chemical warfare agents and pesticides results in the inhibition of acetylcholinesterase and a concomitant inhibition of nerve function due to the buildup of acetylcholine. Treatment of this type of poisoning involves administering 2-hydroxyiminomethyl-1-methylpyridinium (2-PAM) to reactivate the inhibited enzyme and an antimuscarinic agent (such as atropine) to antagonize the actions of excess acetylcholine.

Antidotal therapy with antimuscarinic agents is difficult to manage because these compounds are quite toxic and can have serious side effects. Thus, although the effective treatment of anticholinesterase poisoning may require 20 to 50 mg of atropine in the first day,[1] soldiers at risk are issued injectors containing only 2 mg because of the antidote's extreme toxicity.[2] Other muscarinic antagonists, such as benactyzine and quinuclidinyl benzilate (QNB), are better antidotes than atropine, but are not used extensively because of their severe side effects.

The toxicity of atropine is inherent in its mode of action. To counteract the action of the excess acetylcholine that results from anticholinesterase intoxication, atropine competes with acetylcholine for muscarinic receptors in the nervous system and at peripheral organs. Because the binding of atropine, unlike that of acetylcholine, does not cause nerve impulse or mimic the peripheral actions of acetylcholine, atropine reduces the activity in a poisoned system to a level closer to normal. However, in an unpoisoned system atropine also reduces the level of activity induced by acetylcholine, and because it is metabolized very slowly to inactive components, it continues to poison the system even when the levels of enzyme return to normal. Metabolism studies in man have shown that 50% of the administered dose of atropine is excreted unchanged in the urine. For antidotal purposes, the ideal antimuscarinic drug would be one that is active in the poisoned system, yet inactive when the system is functioning normally.

We initially started work on this problem in 1983 (under USAMRDC Contract No. DAMD17-83-C-3109). We proposed that such an ideal antidote can be designed by incorporating into the molecule, features that allow the antimuscarinic activity of the antidote to be modulated by

the degree of cholinesterase activity. This is accomplished by constructing muscarinic antagonists containing an ester linkage that is susceptible to cholinesterase hydrolysis. When such a compound is administered to a system in which cholinesterase is functioning normally, the compound is degraded to inactive products, rendering it nontoxic. If the cholinesterase has been inhibited, the compound retains antimuscarinic activity and thus acts as an antidote. As cholinesterase activity returns, the drug is removed from the system. The antidote should also not exhibit significant inhibition of cholinesterase since the hydrolytic action of the enzyme is essential in reducing the levels of acetylcholine and returning the system to normal.

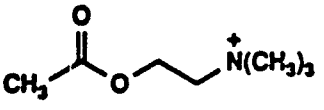
Such a compound has several advantages. First, it could be administered more readily in suspected cases of poisoning without fear of overdose. Second, the side effects would be of a shorter duration, since the drug would only last in the system as long as it was needed. Finally, this type of antidote lends itself to the development of a controlled-release drug that could be administered to personnel at risk, before their exposure to agents, without fear of side effects.

Our research to date has shown that such compounds can be synthesized and that inhibition of cholinesterase prolongs their activity in tissue homogenates.

APPROACH

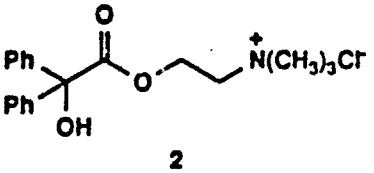
This research is based on the premise that antimuscarinic activity and susceptibility to cholinesterase hydrolysis can be combined in one molecule. The binding sites of cholinesterase [3] and the muscarinic receptor[4,5] have been extensively studied and have several structural requirements in common.

Muscarinic antagonists bind to the muscarinic acetylcholine site but produce no receptor response. As a general rule, substitution of increasingly large hydrocarbon groups on either terminus of acetylcholine (1) leads first to muscarinically inactive compounds and then to muscarinic antagonists.[4,5]



1

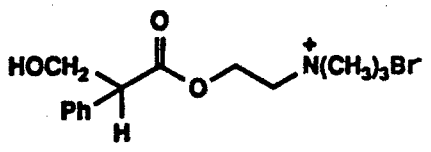
A typical atropine-like anticholinergic agent contains a cationic head and a heavy blocking moiety (cyclic groups), which are connected by a chain of atoms of definite length that generally contains an ester function. The cationic head is an essential group in a large number of anticholinergic compounds and the mechanism of action of such substances has been linked very closely with it. It is assumed that the cationic head with its positive charge is attracted by an anionic site on the muscarinic receptor, which seemingly starts the process of adsorption. Following this attraction, the weaker hydrophobic and dipole-dipole forces go into action to contribute to the stability of the drug-receptor complex. In such an interaction, not only the charge of the cationic head but also its size and shape are vitally important. Thus, successive replacement of the methyl groups of acetylcholine with ethyl groups produces a progressive reduction in muscarinic activity.[6] In contrast, replacing the *N*-methyl groups of *N,N*-dimethylamino-ethylbenzilate methochloride (2) with ethyl groups produces maximal blocking activity.[7]



2

Further increase in size to butyl or larger alkyl groups reduces or abolishes the activity.[5,7-9] Heterocyclic rings such as tropane in atropine also yield high antimuscarinic activity.

At the acyl end of the molecule, the most active anticholinergics contain two cyclic substituents as blocking groups at the same carbon atom (e.g. 2) or one cyclic substituent and a hydroxyl function as exemplified by the esters of tropic acid (e.g. tropinoylcholine 3).[4]



3

The cyclic structure does not necessarily have to be phenyl, since compounds with cyclohexyl rings also show excellent anticholinergic activity and substances containing both rings are even better.[10] The addition of a second phenyl ring into the α-carbon in the acyl portion of tropinoylcholine, however, actually lowers the anticholinergic activity.[4] Planar heterocyclic groups such as thiophenes have also been introduced at the acyl end of the molecule, and these compounds retain anticholinergic activity. It has been suggested that the cyclic groups form an additional contact with the muscarinic receptor by hydrophobic or van der Waals forces. As a result, this contact is strengthened and the muscarinic receptors are protected from approaching molecules of acetylcholine.

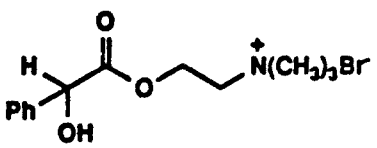
The presence of the cationic head and of cyclic blocking groups is not sufficient for optimal anticholinergic activity; the activity also depends on the mutual distribution of these groups. Several studies[7,9,11] have shown that the linking chain containing a potentially hydrolyzable ester should be of the form CCOCC, with no alkyl substitution on the carbons α or β to the nitrogen for high anticholinergic activity.

The successful antidote will incorporate the above features into a molecule that can be hydrolyzed by cholinesterase. The optimal system would use acetylcholinesterase as the hydrolytic enzyme. However, this enzyme will not accommodate the structural features necessary for muscarinic antagonism. Fortunately, serum cholinesterase is inactivated by anticholinesterase agents at rates similar to the rate of acetylcholinesterase inactivation and hydrolyzes a broader range of substrates.[3,12]

Serum cholinesterase hydrolyzes choline esters containing a variety of hydrophobic acyl groups. Large, aromatic acyl groups have a higher affinity for the enzyme, and in some cases this tighter binding is accompanied by a lower hydrolytic rate. The enzyme is more sensitive to the structure of the choline moiety. Addition of an α- or β-methyl group to choline or increasing the distance from the nitrogen to the ester linkage both cause a dramatic loss of binding affinity of butyrylcholine to the enzyme. Cholinesterase is also very sensitive to the size of the choline "head" in that larger structures have lowered affinity, suggesting that the dimensions of the anionic center in the enzyme are limited.[3]

The binding specificities for cholinesterase hydrolysis and muscarinic antagonism suggest a family of compounds containing aryl, hydroxyl-containing carboxylic acids linked to choline derivatives. Many compounds that fall into this group have been previously synthesized but few have been tested for effectiveness as antidotes for organophosphorous CW agents.

The simplest such compounds and the lead compounds for this study are the R-(+)- and S-(-)- forms of tropinoylcholine (3)[13] and the S-(+)- and R-(-)- forms of mandeloylcholine (4).[14]



4

These compounds are reversible competitive antagonists of acetylcholine at the muscarinic receptors of the guinea pig ileal longitudinal muscle, and one molecule of the antagonist competes with one molecule of the agonist at each site. Their affinity for the muscarinic receptor site is weaker than that for atropine, but they do exhibit the important property of acting as substrates for cholinesterase and being hydrolyzed, albeit slowly, by the enzyme. Both groups of compounds were stereoselective for the muscarinic receptor sites and for cholinesterase, with the (-) configuration exhibiting greater affinity for the receptor site than the (+) configuration and the opposite being the case for the enzyme. These results suggest that the esteratic site of the muscarinic receptor and of cholinesterase may be stereoselective.

In our research we have reasoned that the most effective antidotes would probably have a higher level of antimuscarinic activity and perhaps a slower rate of hydrolysis than mandeloylcholine. It should be remembered that slow hydrolysis for this class of compounds still

probably removes them from the circulation much faster than atropine is removed. From the information available on the binding sites involved, we suggested modifications in the choline head group, in the hydrogen-bonding group of the carboxylic acid moiety, and in the structure of the aromatic ring.

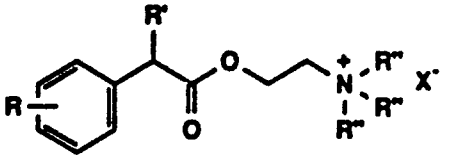
Our *in vitro* results to date (under Contract No. DAMD17-83-C-3109) following the synthesis of a variety of compounds (under Contract Nos. DAMD17-83-C-3109 and DAMD17-85-C-5147), 23 of which have been evaluated *in vivo* by the USAMRICD, have provided insight into how variations in the structure of **3** and **4** affect muscarinic antagonism and cholinesterase hydrolysis.

The data in Table 1 shows how the binding affinity for the muscarinic receptor depends on the structure of the amino group for *N,N*-dialkylaminoethyl esters of (+)- and (-)-mandelic and tropic acids. It is clear that the extra methylene group in tropic acid significantly increases the affinity and stereoselectivity of all the esters tested, with the quaternized derivatives of the diethylaminoethyl esters providing consistently lower values of K_i and therefore higher affinities for the receptor. The esters quaternized with alkyl iodides show better affinity for the receptor than do the hydrochlorides in all our *in vitro* tests.

Table 2, which compares the *in vivo* and *in vitro* data for the quaternary salts of the *N,N*-dialkylaminoethyl esters of tropic acid, previously tested by USAMRICD, shows that administration of nine of the compounds resulted in some mice being saved and two were of interest, saving significantly more mice than did atropine. At this point it is difficult to see a firm correlation between the biochemical properties of the compounds and their *in vivo* activity, but several trends seem to be present. Compounds that are hydrolyzed slowly are more likely to be effective, as are compounds that have a higher affinity for the muscarinic receptor. Furthermore, compounds with very high or low toxicities are less likely to be effective.

Table 1

In vitro Muscarinic Receptor Binding Affinities (K_i) of
2-*N,N*-Dialkylaminoethyl Esters of Mandelic and Tropic Acids



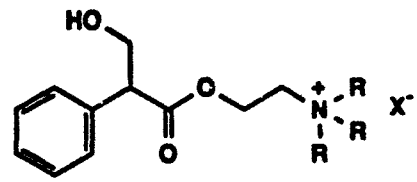
		K_i (nM)			
		Mandelic Acid (R'=OH)		Tropic Acid (R'=CH_2OH)	
R	R" Amine	(+)-isomer	(-)-isomer	(+)-isomer	(-)-isomer
H	NMe_2.HCl	42,000	28,000	280	8.5
H	NMe_3I	1,000	2,000	52.5	5.5
H	NMe_2EtI	1,020	400	15	0.7
H	NEt_2.HCl	50,000	18,000	55	2.4
H	NEt_2MeI	800	290	37	1.5
H	NEt_3I	NA	240	20	0.7
H	pyrrolidine.HCl	NA	NA	55	200
H	morpholine.HCl	NA	NA	NA	66
4-MeO	NMe_2.HCl	NA	NA	650[a]	
1-Naphthyl	NMe_2.HCl	NA		80[a]	
1-Naphthyl	NMe_3I	NA		40[a]	
1-Naphthyl	NEt_2.HCl	NA		213[a]	
H	NMe_3I	NA	NA	110[b]	750[b]
Acetylcholine			3,500		
Atropine			0.32		

[a] (±)Mixture

[b] R' = $(OH)CH_2OH$

Table 2

Comparison of *In vitro* data with *In vivo* Intramuscular Anticholinergic Survival Efficacy data[a] for 2-*N,N*-Dialkylaminoethyl Tropic Acid Esters in the Mouse



AMINE	ISOMER	Musc. Bind K_i(nM)	Cholin. Hydrol. t ($^1/_2$)min.	IM LD_{50} (mg/kg)	1/16	1/8	1/4
NMe_2.HCl	(+)	280	>120	100	0	0	0
NMe_2.HCl	(-)	8.5	>120	1970	0	1	1
NMe_3I	(+)	52.5	5	736	0	0	0
NMe_3I	(-)	5.5	15	560	0	1	0
NMe_2EtI	(+)	15	>120	180	0	0	0
NMe_2EtI	(-)	0.7	30	940	0	0	0
NEt_2.HCl	(+)	55	NA	NA	NA	NA	NA
NEt_2.HCl	(-)	2.4	60	NA	NA	NA	NA
NEt_2MeI	(+)	37	>120	455	0	0	4
NEt_2MeI	(-)	1.5	>120	243	2	2	2
NEt_3I	(+)	20	>120	1616	0	0	0
NEt_3I	(-)	0.7	>120	284	1	1	3
pyrrolidine.HCl	(+)	55	NA	2420	1	1	0
pyrrolidine.HCl	(-)	200	NA	>400	0	0	1[b]
piperidine.HCl	(+)	NA	NA	2432	1	0	0
morpholine.HCl	(-)	66	NA	>361.5	0	1	0[c]

[a] Compound administered with 2-PAM after GD challenge, at doses equal to the indicated fraction of the LD_{50}. Corrected number of survivors out of 10 is indicated.

[b,c] Dose fractions [b]1/256 1/32 1/4 [c]1/64 1/16 1/4.

RESULTS AND DISCUSSION

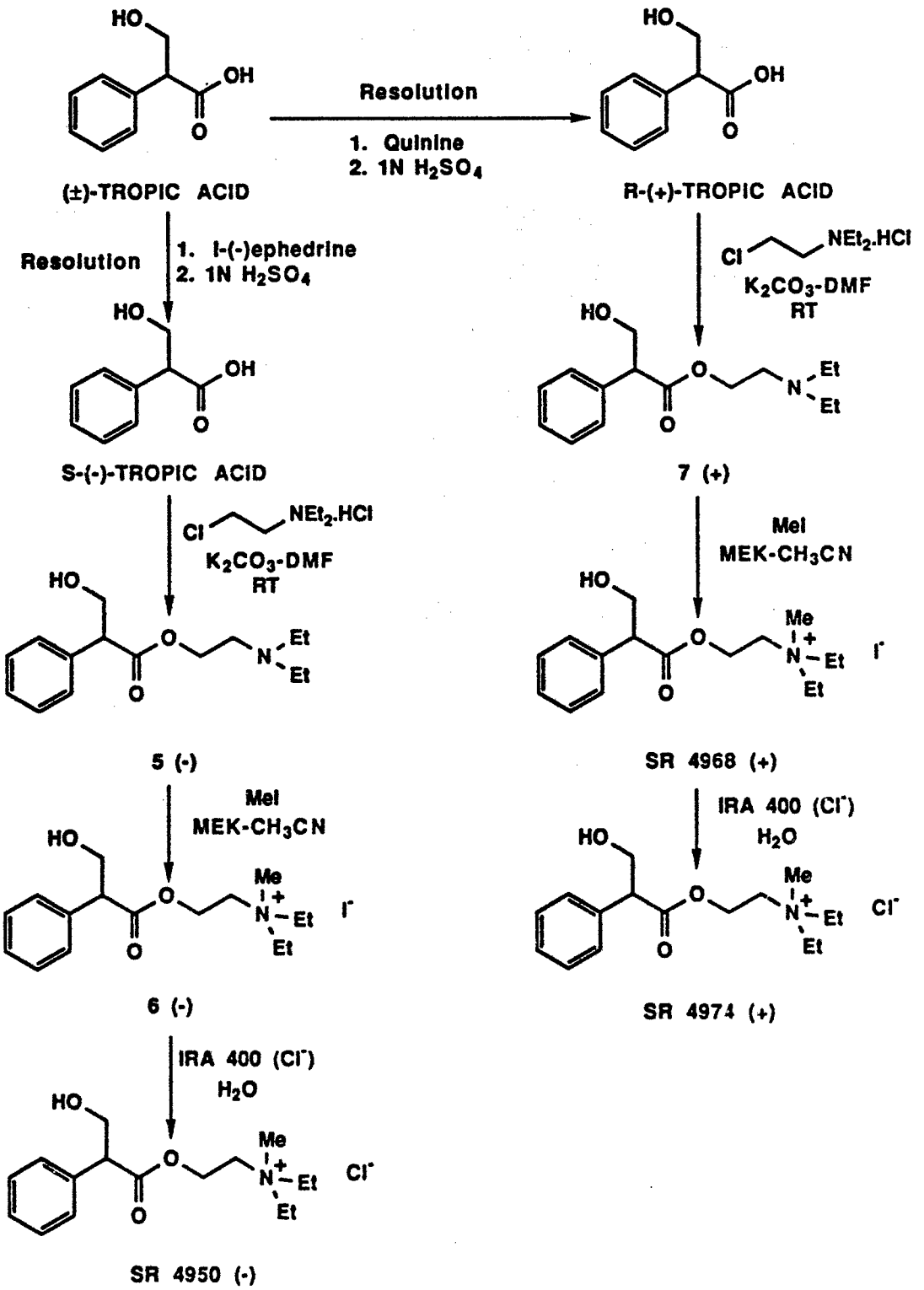
Chemistry

The data from the *in vitro* muscarinic binding studies shown in Table 1 clearly demonstrates the stereoselective specificity of the muscarinic receptor for the S-(-)-isomers of the quaternary salts of the *N,N*-dialkylaminoethyl esters of tropic acid. It is also clear that the presence of the extra methylene group in tropic acid, compared to mandelic acid, significantly increases the affinity and stereoselectivity of all the esters tested, with the quaternized derivatives providing consistently lower values of K_i and therefore higher affinities for the receptor.

It was therefore decided to continue to investigate the tropic acid derivatives, as outlined in the Statement of Work for this contract (Compounds **28-35**), and to concentrate on the synthesis and *in vitro* and *in vivo* testing of esters of S-(-)-tropic acid. Careful choice of the alkyl substituents on the onium end of the molecule should produce muscarinic binding affinity superior to that of atropine, while still yielding a molecule which can be readily hydrolyzed to inactive components by cholinesterase These two factors are of paramount importance in the design of drugs which will be more effective than atropine as antidotes for antimuscarinic agents.

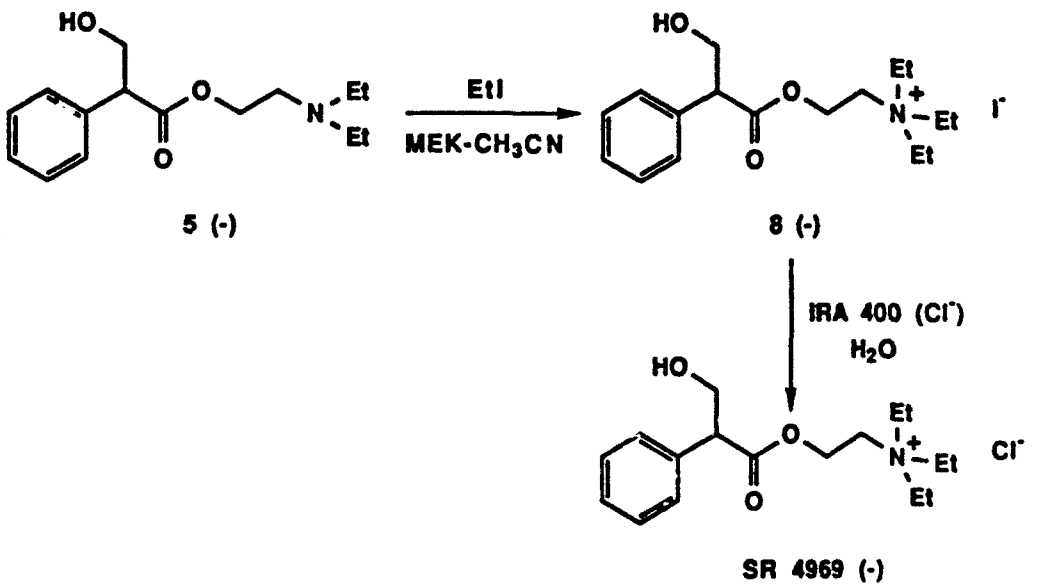
Resolution of (±)-tropic acid was completed on a large scale (200g) using methodology previously carried out on a small scale at SRI International (Scheme 1). Initial reaction of (±)-tropic acid with quinine in ethanol gave the R-(+)-tropic acid quinine salt as a white crystalline solid which on recrystallization and treatment with 1N H_2SO_4 yielded R-(+)-tropic acid with an optical purity of 98%, in 28% overall yield. Concentration of the combined filtrates from the initial reaction and subsequent recrystallizations, followed by acidification yielded a mixture enriched in S-(-)-tropic acid. Treatment with l-(-)-ephedrine in 60% aq. ethanol, recrystallization of the salt formed, and acidification, gave S-(-)-tropic acid also in good yield (49%) and in high optical purity (~100%).

Reaction of S-(-)-tropic acid with 2-*N,N*-diethylaminoethyl chloride hydrochloride using reaction conditions optimized by us in previous syntheses (K_2CO_3-DMF, RT) gave the 2-*N,N*-diethylaminoethyl ester (**5**) in 77% yield. Reaction with MeI gave the methoiodide (**6**) which was converted into the methochloride (**SR 4950**) by passage down an IRA 400 (Cl^-) ion exchange resin column. Recrystallization of the lyophilized material gave product which retained the high optical purity of the parent acid ($[\alpha]_D$=-21°).


(±)-TROPIC ACID
Resolution
1. Quinine
2. 1N H_2SO_4
R-(+)-TROPIC ACID
Resolution
1. l-(-)ephedrine
2. 1N H_2SO_4
S-(-)-TROPIC ACID
Cl NEt2.HCl
K_2CO_3-DMF
RT
7 (+)
Cl NEt2.HCl
K_2CO_3-DMF
RT
5 (-)
MeI
MEK-CH_3CN
SR 4968 (+)
MeI
MEK-CH_3CN
6 (-)
IRA 400 (Cl^-)
H_2O
SR 4974 (+)
IRA 400 (Cl^-)
H_2O
SR 4950 (-)

Scheme 1

Quaternization of 5 with ethyl iodide (2-butanone-CH_3CN) gave the ethoiodide (8) which could not be crystallized. However, conversion into the ethochloride (SR 4969), by passage of the compound down an IRA 400 (Cl^-) ion exchange resin, and recrystallization of the lyophilized residue gave product as white crystalline needles (Scheme 2).



Scheme 2

Resynthesis of R-(+)-α-(hydroxymethyl)benzeneacetic acid, 2-*N,N*-diethylaminoethyl ester methoiodide (SR 4968, Scheme 1), the most active derivative tested by USAMRICD *in vivo* in combination with 2-PAM after GD challenge, and its conversion into the less toxic methochloride (SR 4974) was carried out. The synthesis followed closely that described for the S-(-)-isomer (SR 4950) and the product was isolated in 57% overall yield.

Considerable investigation into HPLC methodology necessary for the confirmation of the purity of samples synthesized as part of this contract was carried out on the two methoiodides (6) and (SR 4968) but without success. The purchase of HPLC columns, sold by Rainin, and described as being capable of separating optically active isomers suggested that we might be able to use HPLC to confirm whether optically pure starting materials, intermediates or products were

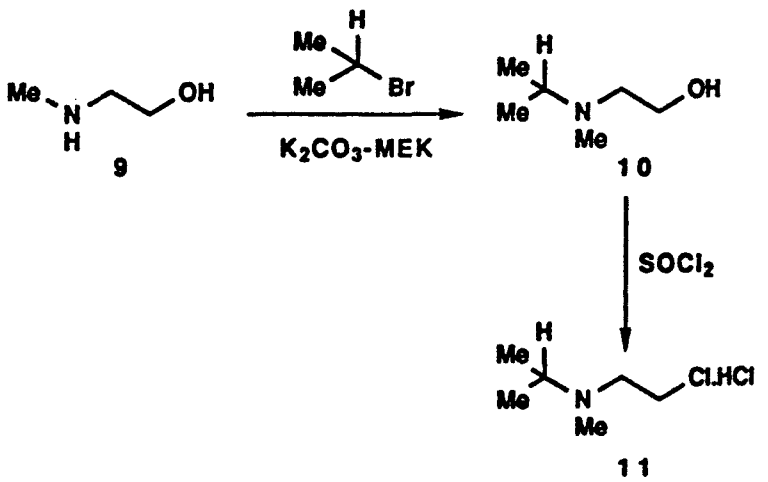
undergoing any racemization during the synthesis of targets. Unfortunately chromatographic separation of pure compounds **6** and **SR 4968** and mixtures of the two compounds was poor using a variety of mobile phases and yielded little information that could not be obtained from measurement of the $[\alpha]_D$ values. When samples of the two compounds were sent to Rainin they were unable to improve upon the disappointing resolution we had obtained. This approach to determining optical purity of the products was therefore discontinued.

During the course of the research on the ion exchange process we have found that there were instances when analytical analysis of the methochlorides produced (e.g. **SR 4950**) clearly showed that the process of converting the iodides into chlorides i.e. by passage down an IRA 400 (Cl^-) ion exchange resin column, had not gone to completion. In order to expedite the analytical process, since the ion exchange methodology is such an integral part of the synthesis of the majority of the products in this contract, we developed a color test to determine whether a product was pure. The test was a very simple one. A small quantity of the product was dissolved in an acid solution of soluble starch, addition of a few drops of 30% H_2O_2 then immediately indicated the presence of any iodide in the sample by the formation of a dark color due to the presence of I_2. We have now used this test extensively to analyze products and found it to be a good indicator of complete conversion of iodides into chlorides.

Cusic and Robinson have shown[15] that the introduction of *iso*-propyl groups into the onium terminus of the quaternary salts of 2-*N*,*N*-dialkylaminoethyl esters of (±)-tropic acid yielded compounds, that exhibited anti-acetylcholine activity that was superior to that of atropine in their test system.

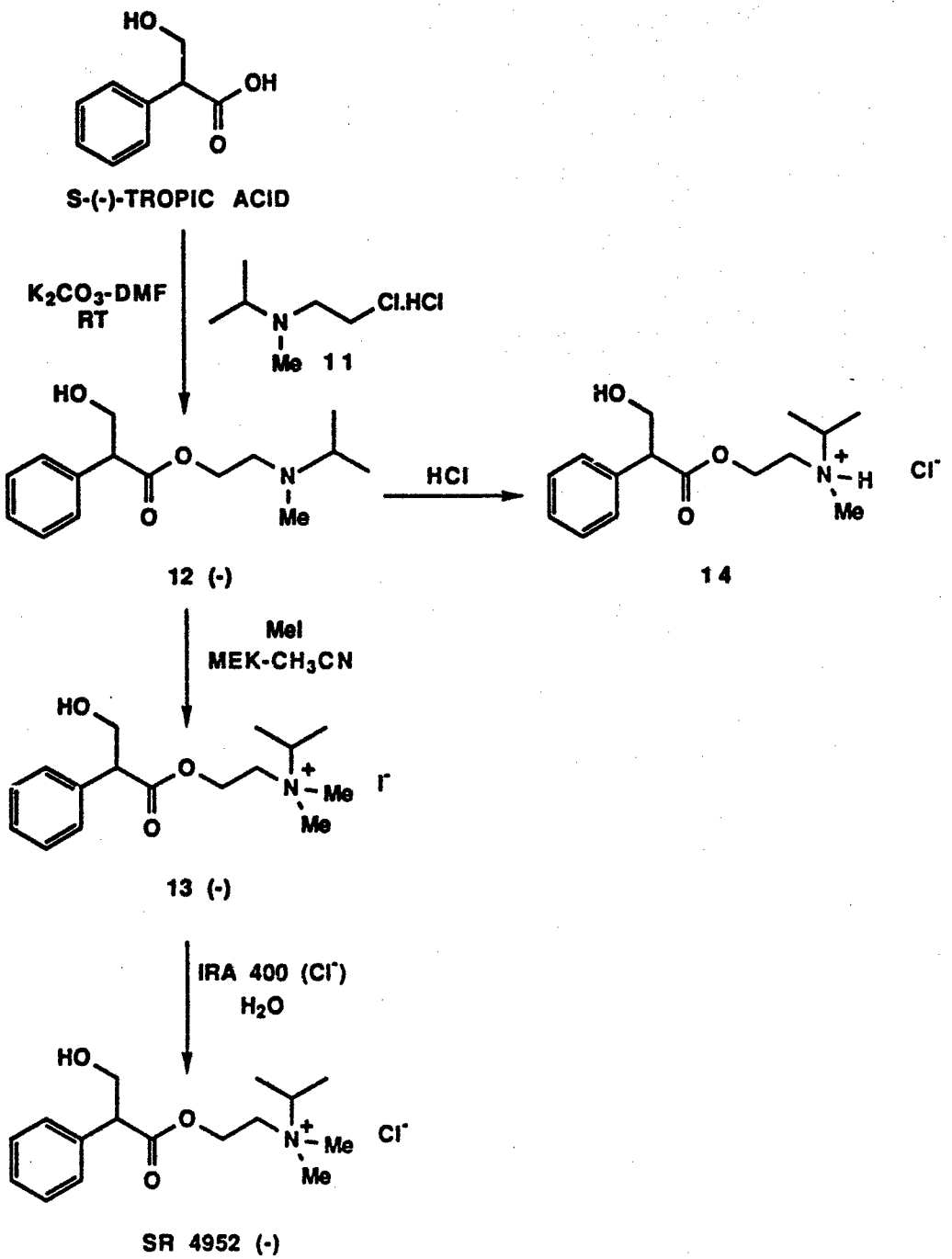
The synthesis of a series of similar compounds (Schemes 3 and 4) incorporating 1 or 2 *iso*-propyl groups starting from S-(-)-tropic acid was therefore initiated, in order to carry out *in vitro* tests to determine the binding affinity of these agents for the muscarinic receptor and their rate of hydrolytic cleavage by cholinesterase. Careful analysis of these data will give us an indication as to whether these agents will possess the necessary *in vivo* activity we are attempting to potentiate.

Synthesis of these two series of compounds was carried out using the methodology we have previously developed at SRI International. The appropriate chloride, 2-*N*-*iso*-propyl-*N*-methylaminoethyl chloride hydrochloride (**11**), was synthesized, as shown below, in good yield.

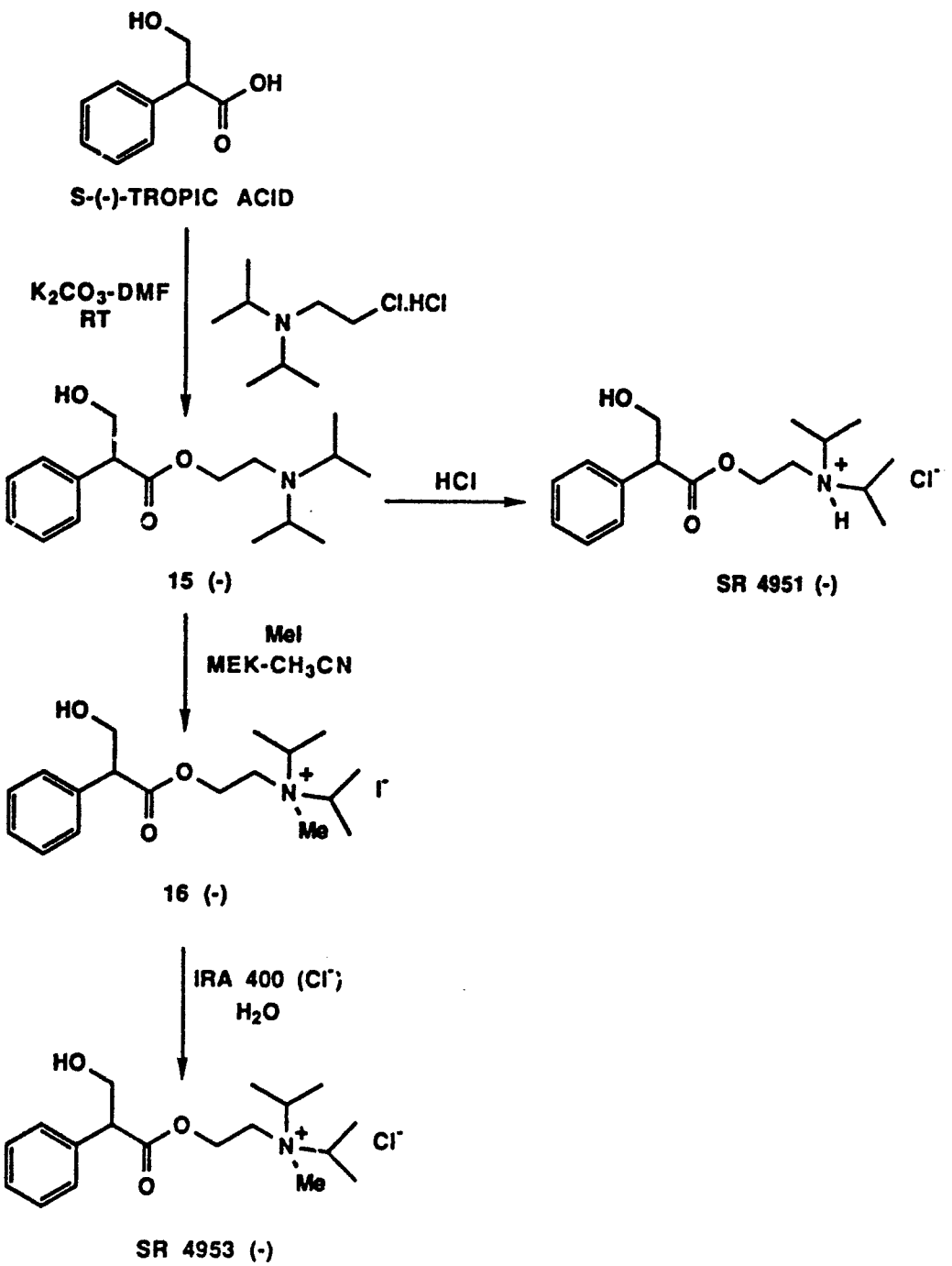


Reaction of **11** with S-(-)-tropic acid, employing usual conditions (Scheme 3), gave the 2-*N-iso*-propyl-*N*-methylaminoethyl ester (**12**) in 77% yield. Acidification with gaseous HCl-Et_2O gave an oil (**14**) which did not crystallize. Examination of the product by ^1H NMR at 400MHz showed the presence of two diastereoisomers. Attempted separation of the two isomers by normal chromatographic techniques proved unsuccessful. Reaction of **12** with methyl iodide gave the methoiodide salt (**13**) as a pure isomer which was converted into the methochloride (SR 4952).

The second series of targets incorporating two *iso*-propyl groups (Scheme 4) were synthesized from commercially available 2-*N,N*-di-*iso*-propylaminoethyl chloride hydrochloride. Reaction with S-(-)-tropic acid under usual conditions gave the 2-*N,N*-di-*iso*-propylaminoethyl ester (**15**) in 68% yield. Acidification with gaseous HCl-Et_2O gave the hydrochloride (SR 4951) as a white crystalline solid. Reaction of **15** with methyl iodide gave the methoiodide salt (**16**) which was converted into the methochloride (SR 4953) by passage down an IRA 400 (Cl^-) ion exchange resin.


HO
OH
O
S-(-)-TROPIC ACID
K_2CO_3-DMF
RT
Cl.HCl
N
Me 11
HO
O
O
N
Me
12 (-)
HCl
HO
O
O
N+ H
Me
Cl-
14
MeI
MEK-CH_3CN
HO
O
O
N+ Me
Me
I-
13 (-)
IRA 400 (Cl^-)
H_2O
HO
O
O
N+ Me
Me
Cl-
SR 4952 (-)

Scheme 3


HO
OH
O
S-(-)-TROPIC ACID
K_2CO_3-DMF
RT
Cl.HCl
N
HO
O
O
N
15 (-)
HCl
HO
O
O
N
+
H
Cl⁻
SR 4951 (-)
MeI
MEK-CH_3CN
HO
O
O
N
+
Me
I⁻
16 (-)
IRA 400 (Cl^-)
H_2O
HO
O
O
N
+
Me
Cl⁻
SR 4953 (-)

Scheme 4

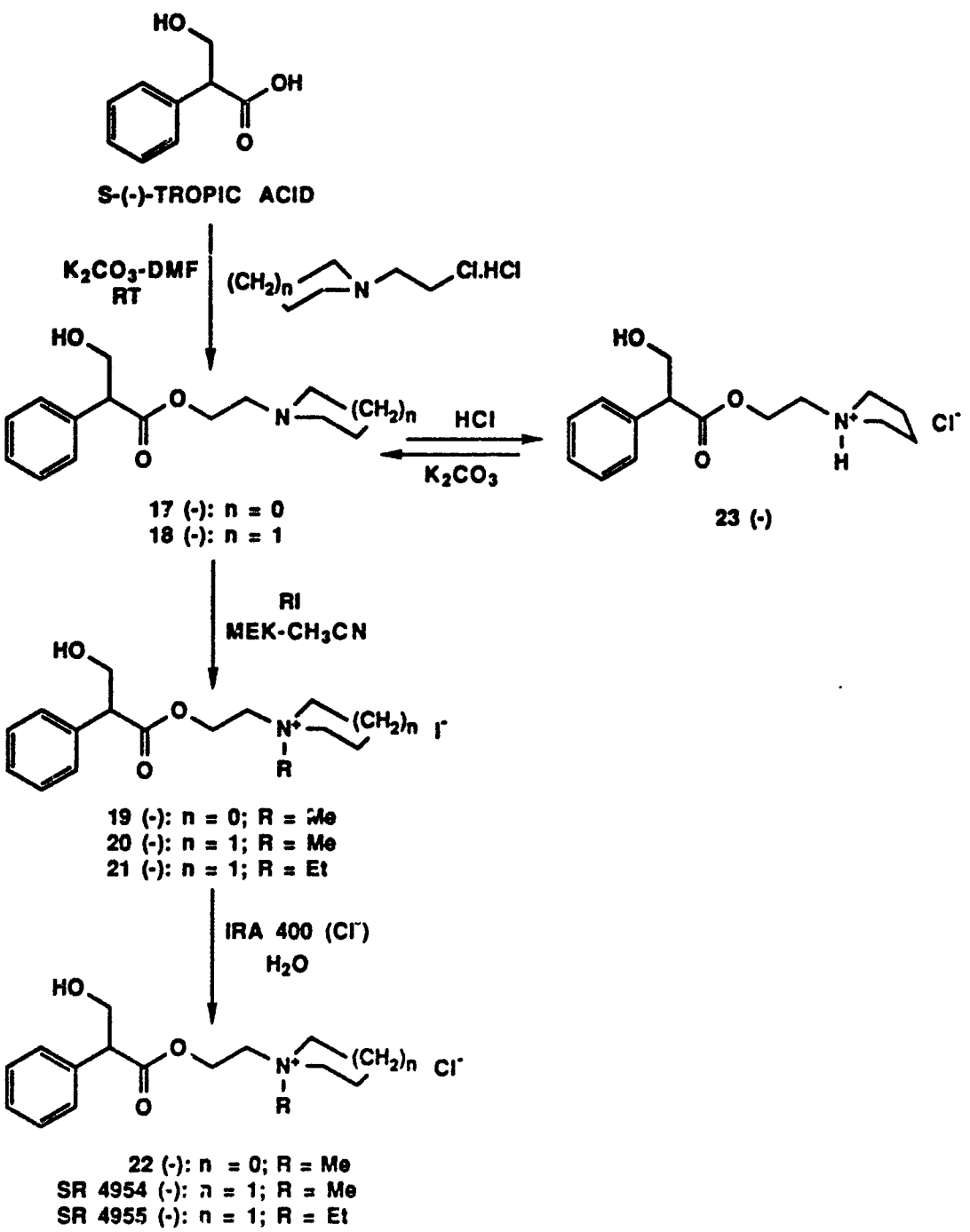
We have also completed, the synthesis of several esters of S-(-)-tropic acid (Scheme 5) incorporating cyclic moieties into the onium end of the molecule. These targets mimic the shape of the more potent analogs investigated by Cusic and Robinson.[15]

Reaction of 1-(2-chloroethyl)pyrrolidine hydrochloride with S-(-)-tropic acid under normal conditions gave the ester (**17**) in low yield (45%), after careful chromatography (Scheme 5, n = 0). Treatment with gaseous HCl in Et_2O had previously been shown to yield a crystalline hydrochloride (**23**). However reaction of **17** with methyl iodide on work-up only gave a yellowish oil (**19**). All attempts to prepare this compound more carefully from extremely pure starting material, or to crystallize the oil, failed, as did attempts to crystallize the methochloride (**22**) formed from passage of the oil down an IRA 400 (Cl^-) ion exchange resin. At this stage, concern over the purity of intermediate (**17**), even though it was shown to be pure by elemental analysis, led us to repurification and formation of the crystalline hydrochloride (**23**). Double recrystallization gave very pure material, which was converted into a diethyl ether solution of (**17**) by treatment with potassium carbonate and careful extraction. All attempts to obtain crystalline material after reaction with methyl iodide and conversion to the methochloride (**22**) failed, even though the target was shown to be analytically pure and anhydrous. Synthesis of targets of this type was therefore discontinued.

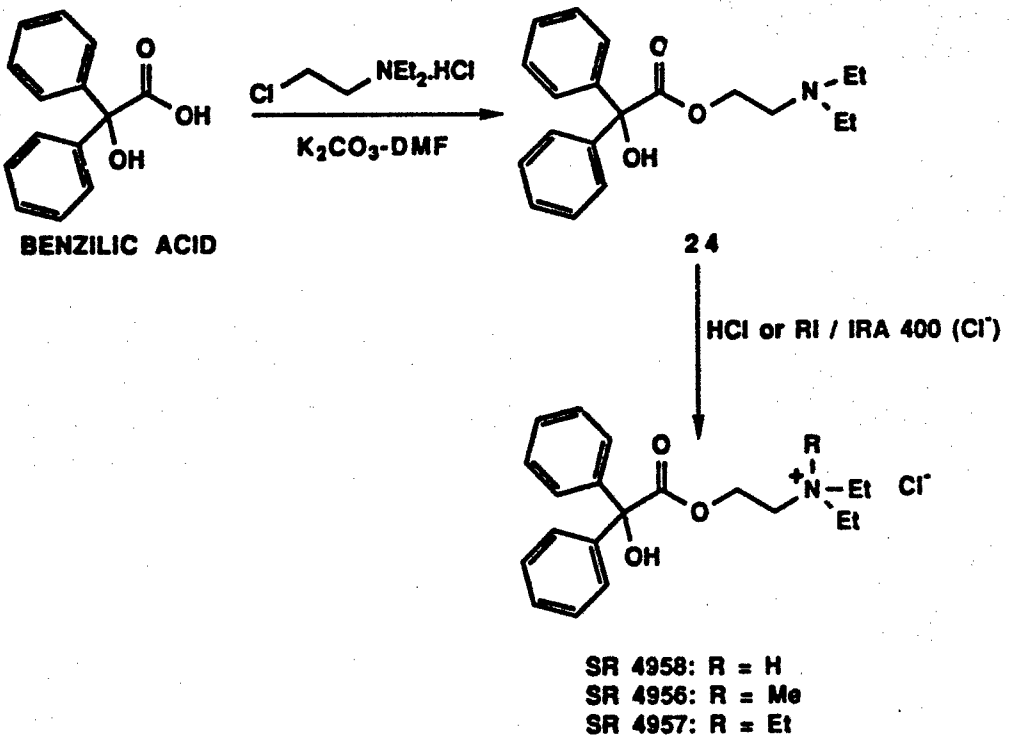
On the other hand the products formed by incorporating a piperidine ring into the targets (Scheme 5, n = 1), crystallized and could be readily recrystallized from *iso*-propanol/2-butanone. The synthesis of two targets, **SR 4954** and **SR 4955**, using standard conditions, is outlined in Scheme 5.

A series of three quaternary salts of 2-*N*,*N*-diethylaminoethyl esters of benzilic acid has also been completed as outlined in Scheme 6. Abramson *et al.*[5] have shown that derivatives of this type bind more strongly than tropic acid derivatives to the postganglionic ("muscarine-sensitive") acetylcholine receptors in the guinea-pig ileum.

During this reporting period we initiated research to synthesize quaternary salts of novel esters of S-(-)-tropic acid incorporating *N*-methylpyrrolidine and *N*-methylpiperidine terminal functions linked by suitable side chains through the 2 and 3 positions respectively, as shown in Schemes 7 and 8. These compounds were designed to attain better muscarinic receptor binding affinity by incorporating an onium head group somewhat similar to that present in atropine while still being able to undergo hydrolysis by cholinesterase.

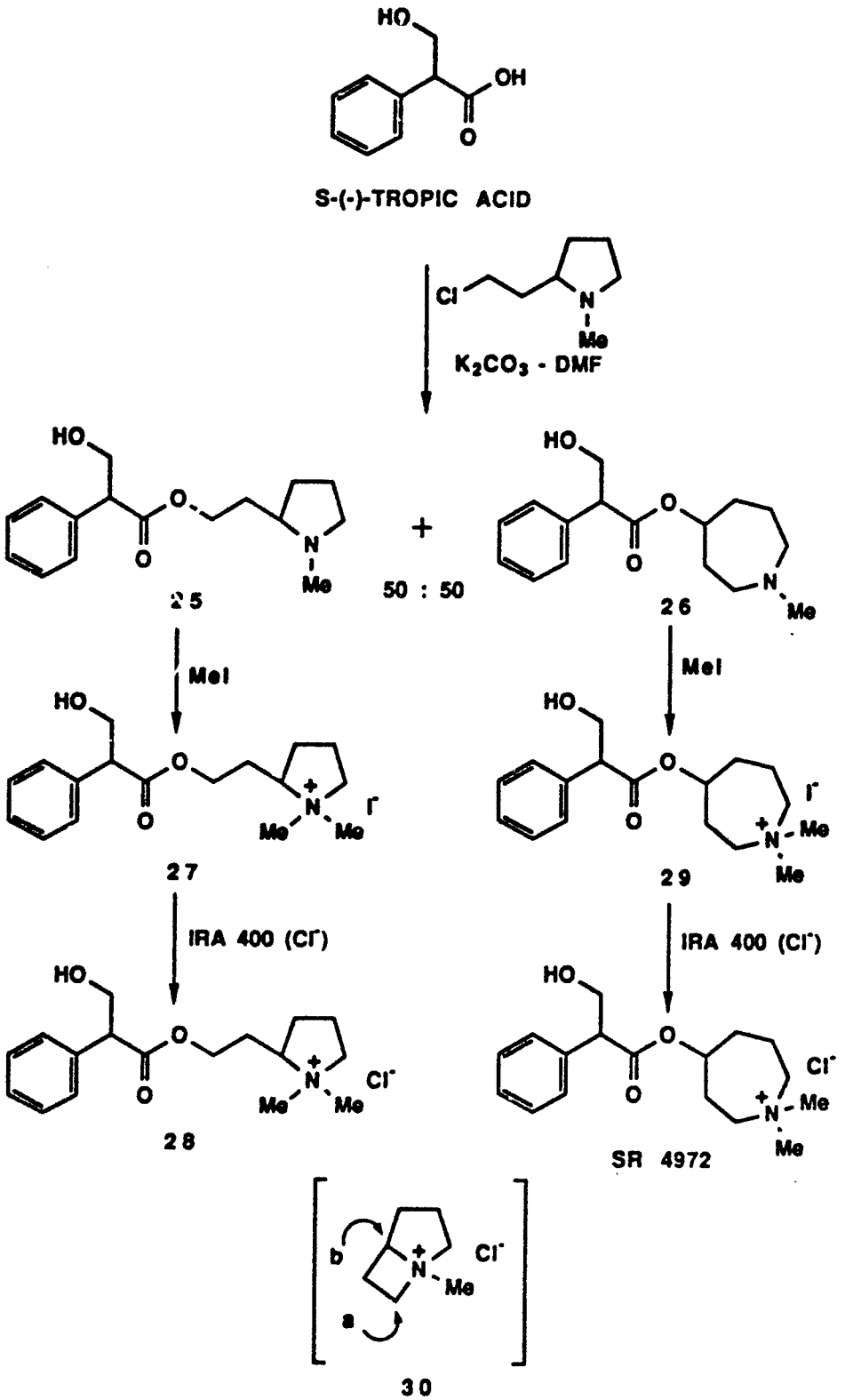

S-(-)-TROPIC ACID
K2CO3-DMF
RT
Cl.HCl
HCl
K2CO3
17 (-): n = 0
18 (-): n = 1
23 (-)
RI
MEK-CH3CN
19 (-): n = 0; R = Me
20 (-): n = 1; R = Me
21 (-): n = 1; R = Et
IRA 400 (Cl-)
H2O
22 (-): n = 0; R = Me
SR 4954 (-): n = 1; R = Me
SR 4955 (-): n = 1; R = Et

Scheme 5

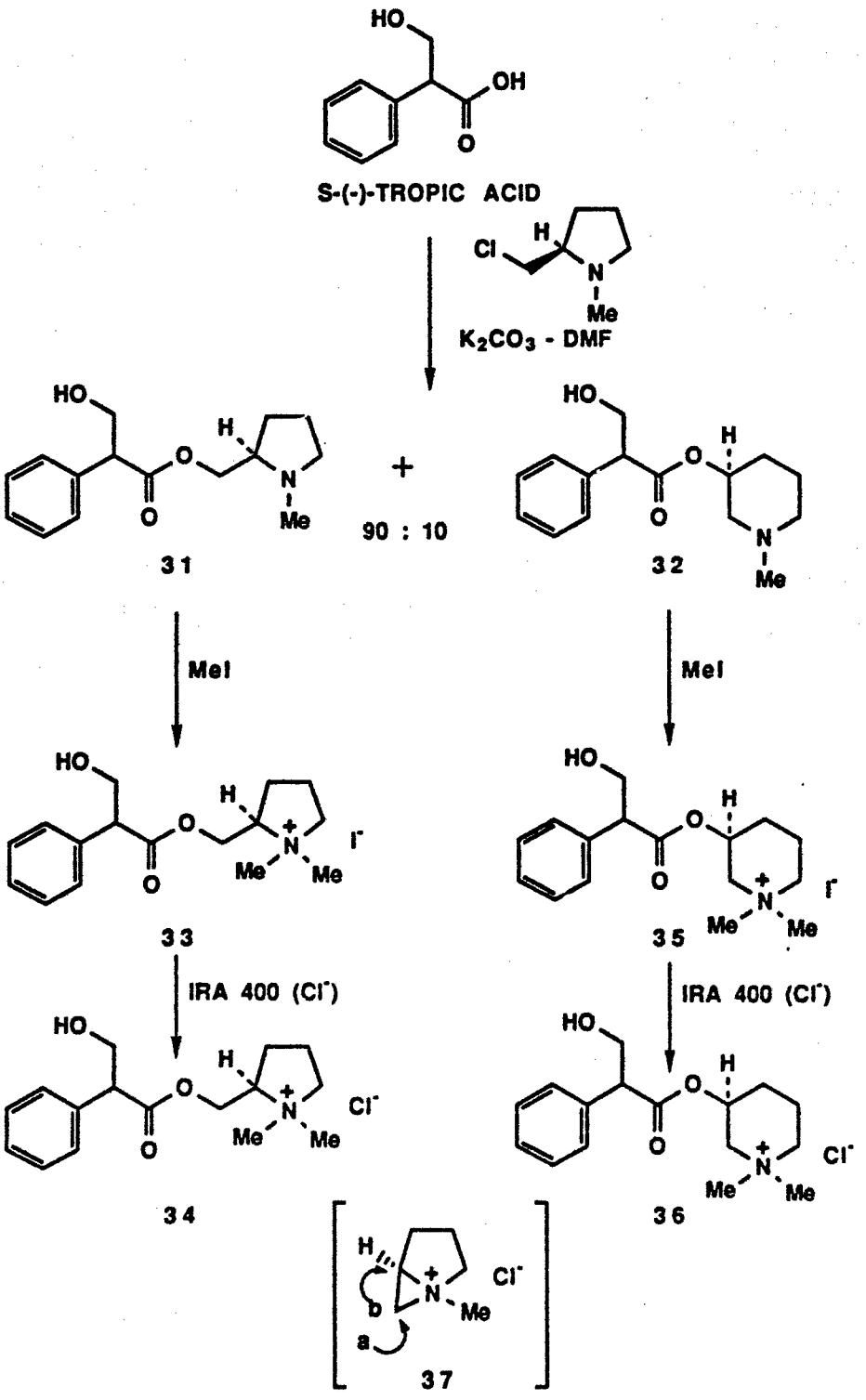


Scheme 6

Initial reaction of S-(-)-tropic acid with racemic 2-(2-chloroethyl)-1-methylpyrrolidine gave a mixture of four diastereomers, instead of the two expected (Scheme 7). High field ^{1}H NMR of the product esters showed the presence of two groups of products in equal ratios, one group containing the pyrrolidine ring (25) and the other group containing a seven membered ring (26). Separation of the two groups of diastereomers by careful chromatography gave pure products as pale yellow oils and subsequent ^{1}H NMR and mass spectral analysis confirmed the assignment. Reaction had clearly proceeded through a bicyclic intermediate (30), formed from the starting material, which had been opened in two directions by the attacking carboxylate nucleophile. Ring opening alpha to the nitrogen from direction a led to the pyrrolidine products (25), while attack at the bridgehead carbon (direction b) led to ring expansion and formation of the hexahydroazepine esters (26). In this case the product ratios indicate that both processes are equally facile. Conversion of ester (25) into the methoiodide (27) proceeded normally, but gave an oil which would not crystallize. Exchange of the iodide for chloride using IRA 400 (Cl^-) ion exchange resin gave the methochloride (28) which likewise remained as an oil. All efforts to obtain this compound in crystalline form have been unsuccessful.


HO
OH
O
S-(-)-TROPIC ACID
Cl
N
Me
K_2CO_3 - DMF
HO
O
O
N
Me
25
+
50 : 50
HO
O
O
N
Me
26
MeI
MeI
HO
O
O
N
Me
Me
I⁻
27
HO
O
O
N
Me
I⁻
Me
Me
29
IRA 400 (Cl⁻)
IRA 400 (Cl⁻)
HO
O
O
N
Me
Me
Cl⁻
28
HO
O
O
N
Me
Cl⁻
Me
Me
SR 4972
b
a
N
Me
Cl⁻
30

Scheme 7

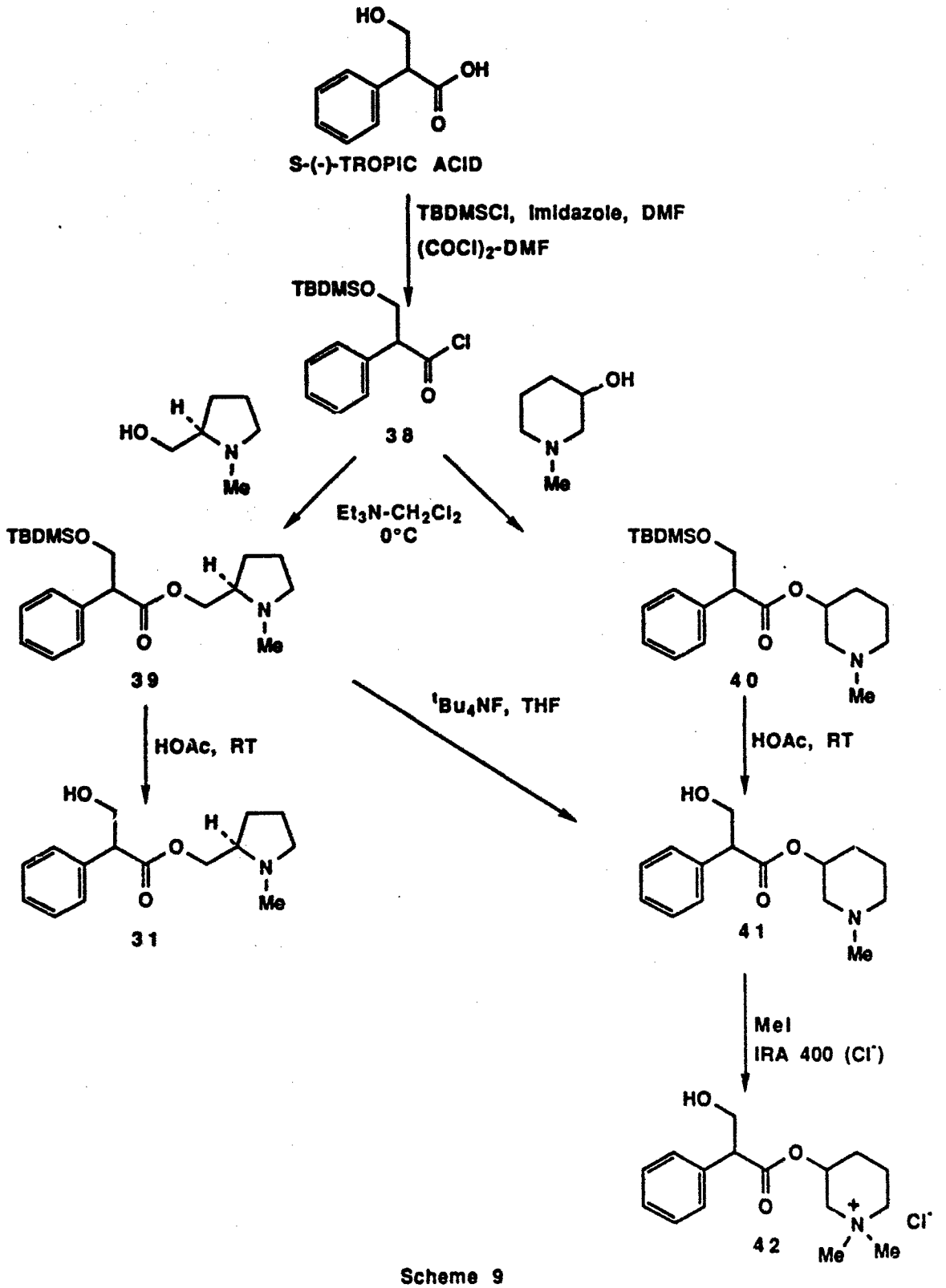

S-(-)-TROPIC ACID
K2CO3 - DMF
90 : 10
31
32
MeI
MeI
33
35
IRA 400 (Cl-)
IRA 400 (Cl-)
34
36
37

Scheme 8

Reaction of the ester of the hexahydroazepine (**26**) with methyl iodide gave the methoiodide (**29**) which was smoothly converted into the white crystalline methochloride (**SR 4972**). Although the product appeared to be pure by high field ^1H NMR and by mass spectral analysis, all attempts to obtain an accurate elemental analysis, even after careful recrystallization, failed. Further purification of the salt proved impossible. Resynthesis and careful purification of the intermediate ester was carried out and conversion into **SR 4972** was completed cleanly as described previously. Extensive recrystallization finally gave an analytically pure sample in sufficient quantity for testing *in vitro*.

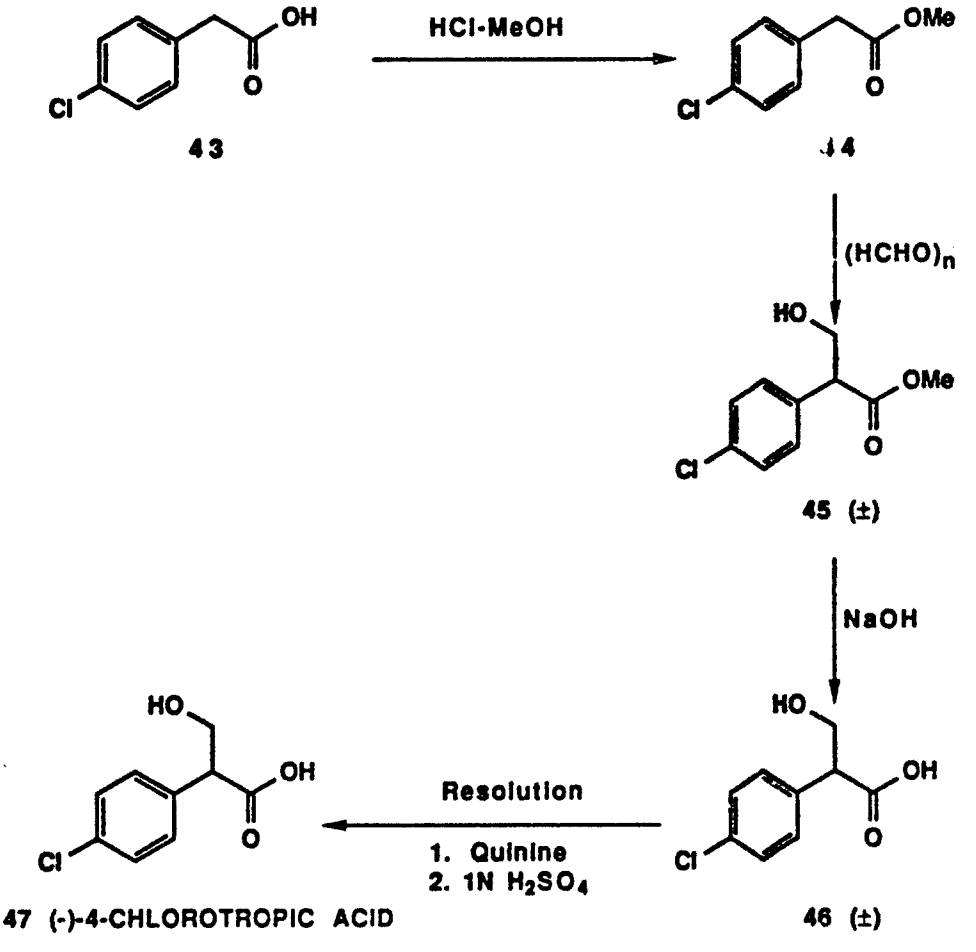
Reaction of S-(-)-tropic acid with pure, optically active S-(-)-2-chloromethyl-1-methylpyrrolidine (Scheme 8) also gave a mixture of two products (**31** and **32**), in a manner somewhat analogous to the previous case. Again reaction proceeded through a bicyclic intermediate (**37**), but this time the product ratio indicated that ring opening was favoured from direction **a** giving the desired product (**31**) as the major component. Separation of the two esters gave the pyrrolidine (**31**) in good yield, as a pale yellow oil, and ^1H NMR and mass spectral analysis confirmed the assignment. Conversion into the methochloride (**34**) proceeded as normal but also gave an oil which could not be crystallized. Research on the synthesis of pyrrolidine esters of S-(-)-tropic acid was therefore discontinued.

A new approach to the synthesis of the S-(-)-tropic acid ester of 3-hydroxy-1-methylpiperidine (**41**) via an acid chloride intermediate (**38**) was next investigated (Scheme 9). Reaction of S-(-)-tropic acid with *t*-butyldimethylsilyl chloride gave the bis-(t-butyl-dimethylsilyl)ester which on treatment with oxalyl chloride gave the protected acid chloride (**38**). Reaction of **38** with S-(-)-1-methyl-2-pyrrolidinemethanol in dichloromethane, in the presence of triethylamine as base, gave the protected ester (**39**). Deprotection with tetrabutylammonium fluoride unexpectedly gave a mixture of diastereomers, which included both the product (**31**) and the ring expanded diastereomeric products (**41**). Presumably the reaction proceeded via cleavage of the ester, formation of a bicyclic intermediate such as **37** (Scheme 8), and subsequent ring opening by the carboxylate anion to give the two types of products. The structure of **41** was confirmed by independent synthesis. Reaction of the protected acid chloride (**38**) with 3-hydroxy-1-methylpiperidine gave the protected ester (**40**) which was deprotected in a mild manner using acetic acid in THF-water to give a mixture of the two diastereomers (**41**). Treatment of the protected pyrrolidine ester (**39**) with the same mild deprotection procedure gave the desired product (**31**) in high yield. Formation of the methochloride (**42**), from **41**, by usual methods


HO
OH
O
S-(-)-TROPIC ACID
TBDMSCl, Imidazole, DMF
(COCl)2-DMF
TBDMSO
Cl
O
38
H
HO
N
Me
OH
N
Me
Et3N-CH2Cl2
0°C
TBDMSO
H
O
O
N
Me
39
TBDMSO
O
O
N
Me
40
tBu4NF, THF
HOAc, RT
HO
H
O
O
N
Me
31
HOAc, RT
HO
O
O
N
Me
41
MeI
IRA 400 (Cl-)
HO
O
O
+
N
Cl-
Me
Me
42

Scheme 9

gave the target in low yield as a white crystalline solid which could not be obtained in analytically pure form. Resynthesis of 42 on a larger scale failed to give any crystalline material and the approach was discontinued.



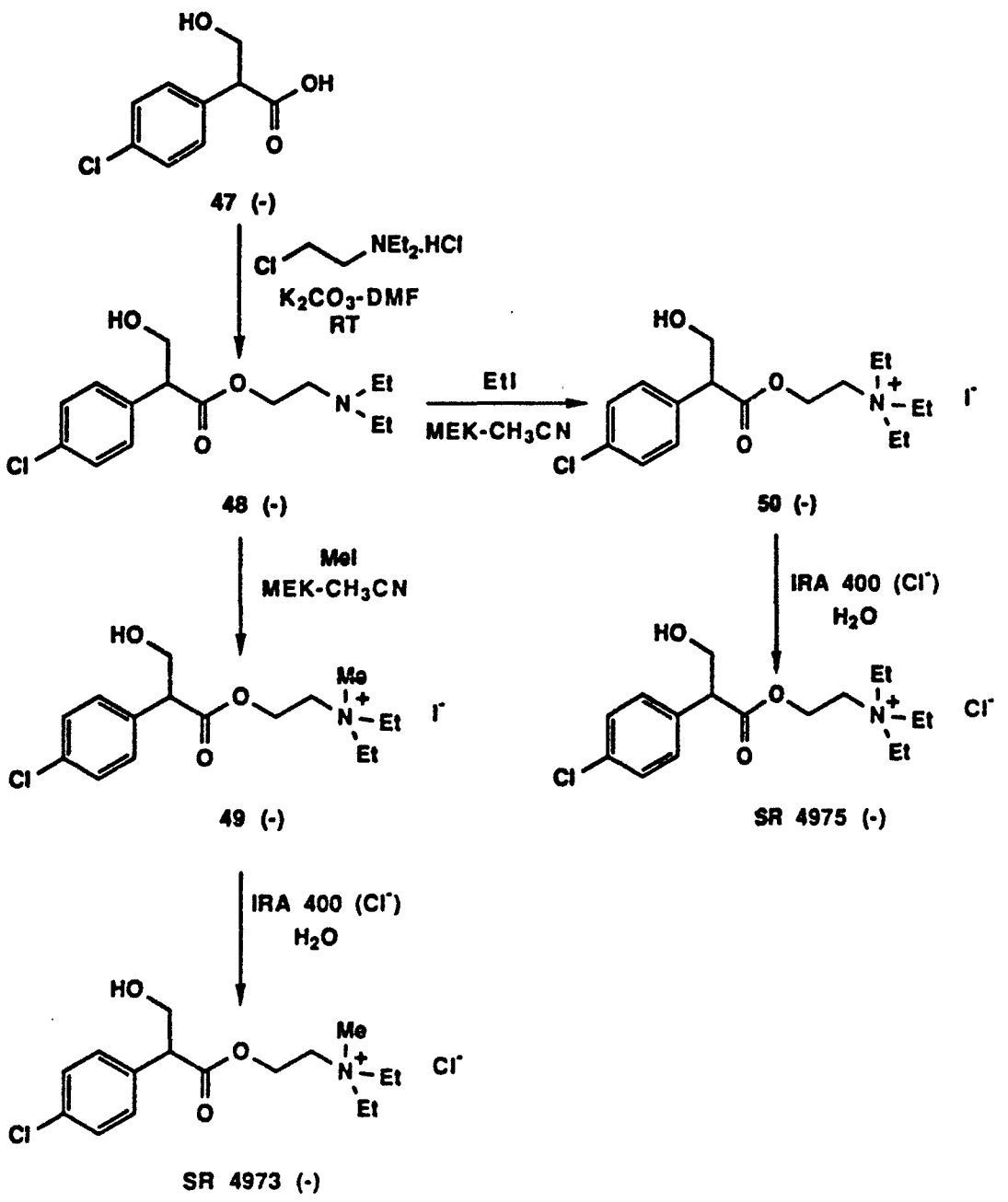
Scheme 10

Since a considerable amount of the research we have carried out to date has focused on the onium terminal end of the esters we are attempting to potentiate, we turned our attention to examining how changes in the aromatic portion of the molecule would affect both the muscarinic receptor binding affinity and the rate of cholinesterase hydrolysis. The initial targets were modified by the introduction of a chlorine atom into the 4-position of the benzene ring portion of the molecule.

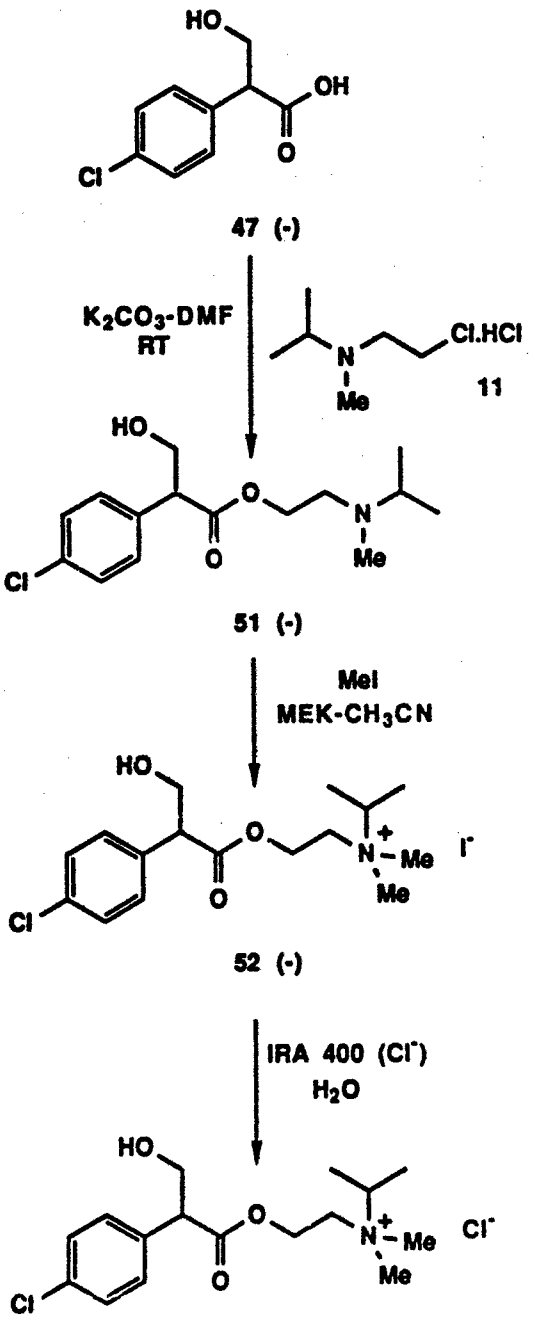
Synthesis of (±)-4-chlorotropic acid (**46**), using methodology previously developed at SRI International, is outlined in Scheme 10. 4'-Chlorobenzeneacetic acid (**43**) was converted into the methyl ester (**44**) by treatment with gaseous HCl in methanol (100%). Reaction with paraformaldehyde in DMSO employing NaOMe as base introduced the hydroxymethyl moiety and cleavage of the ester with NaOH gave (±)-4-chlorotropic acid (**46**) in good overall yield. Resolution of the racemic mixture was carried out in a manner similar to that described for (±)-tropic acid. Formation of the quinine salt, separation of the less soluble diastereomer, recrystallization and acidification with sulphuric acid gave pure (-)-4-chlorotropic acid (**47**). Resynthesis of (±)-4-chlorotropic acid (**46**) on a large scale went according to plan, however, the resolution of the two isomers gave significant problems not previously encountered. Conversion into the quinine salt, separation of the less soluble salt, recrystallization and acidification with sulphuric acid gave (-)-4-chlorotropic acid (**47**) but with an optical purity ($[\alpha]_D$=-46°) considerably lower than the value obtained for the samples previously prepared on a smaller scale ($[\alpha]_D$=-58°). Extensive recrystallization of the quinine salt from a variety of solvents, followed by acidification, failed to produce any samples with better optical purity. Detailed HPLC experimentation and high-field ^{1}H NMR analysis of the (-)-4-chlorotropic acid (**47**) failed to clarify the situation. Finally, recrystallization of the impure acid from ethanol gave a small amount of optically pure product. Extensive reinvestigation of the reaction conditions failed to indicate where the problem lay and therefore the resynthesis was carried out several times on a smaller scale (0.05 mole) to obtain enough (-)-4-chlorotropic acid (**47**), in pure form, to complete the synthesis of the quaternary salts of the 2-*N*,*N*-dialkylaminoethyl esters. No problems were encountered during these reactions although the process was extremely time consuming.

Conversion of (-)-4-chlorotropic acid (**47**) into the 2-*N*,*N*-diethylaminoethyl ester (**48**) was carried out in 71% yield using the normal reaction conditions outlined in Scheme 11. Quaternization with methyl iodide gave the methoiodide (**49**) as a pale yellow oil which crystallized from methylethylketone in 43% yield. Passage down an IRA 400 (Cl^-) ion exchange resin gave the methochloride (**SR 4973**) as a white, analytically pure, hygroscopic solid, which could not be recrystallized. Formation of **SR 4975** employing a similar route using ethyl iodide gave the product as a glass which was crystallized from *iso*-propanol/methylethylketone in low yield (20%).

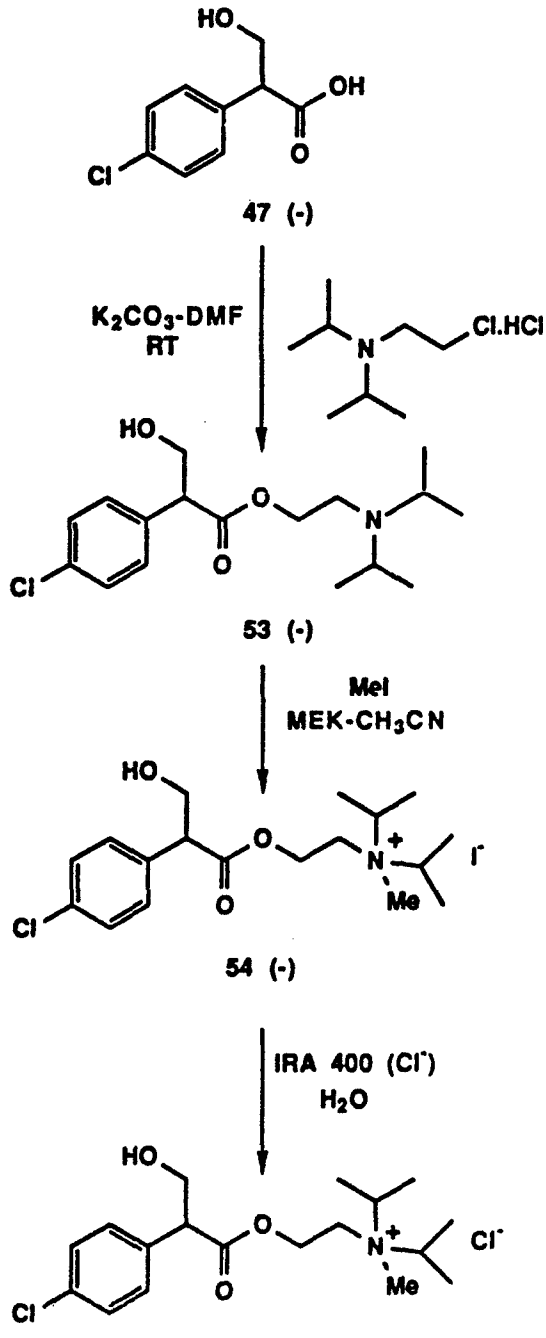
The synthesis of the methochloride of the 2-*N*-*iso*-propyl-*N*-methylaminoethyl ester of (-)-4-chlorotropic acid (**SR 4976**) was carried out as shown in Scheme 12. The appropriate chloride, 2-*N*-*iso*-propyl-*N*-methylaminoethyl chloride hydrochloride (**11**), was resynthesized, as previously described. Reaction of **11** with (-)-4-chlorotropic acid (**47**), employing usual reaction


HO
OH
O
Cl
47 (-)
Cl
NEt2.HCl
K2CO3-DMF
RT
HO
O
O
N
Et
Et
Cl
48 (-)
EtI
MEK-CH3CN
HO
O
O
Et
N+
Et
Et
I-
Cl
50 (-)
MeI
MEK-CH3CN
HO
O
O
Me
N+
Et
Et
I-
Cl
49 (-)
IRA 400 (Cl-)
H2O
HO
O
O
Et
N+
Et
Et
Cl-
Cl
SR 4975 (-)
IRA 400 (Cl-)
H2O
HO
O
O
Me
N+
Et
Et
Cl-
Cl
SR 4973 (-)

Scheme 11


HO
OH
O
Cl
47 (-)
K_2CO_3-DMF
RT
N
Me
Cl.HCl
11
HO
O
O
N
Me
Cl
51 (-)
MeI
MEK-CH_3CN
HO
O
O
N+
Me
Me
I-
Cl
52 (-)
IRA 400 (Cl^-)
H_2O
HO
O
O
N+
Me
Me
Cl^-
Cl
SR 4976 (-)

Scheme 12

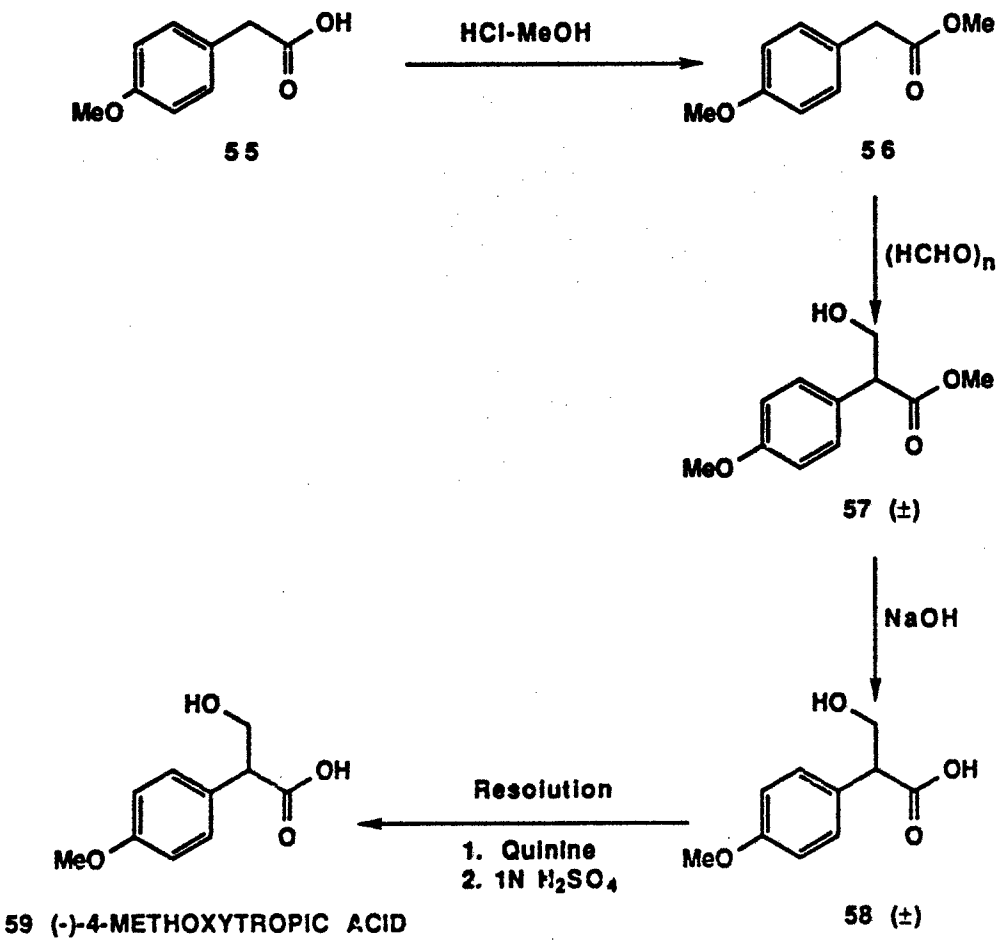


SR 4977 (-)

Scheme 13

conditions gave the 2-*N*-*iso*-propyl-*N*-methylaminoethyl ester (**51**) as a clear oil in 61% yield. Reaction of **51** with methyl iodide gave the methoiodide salt (**52**) in 40% yield as a pale yellow solid. Passage down an IRA 400 (Cl^-) ion exchange resin followed by recrystallization gave SR **4976** (91%).

The second target incorporating two *iso*-propyl groups (Scheme 13) was synthesized from commercially available 2-*N*,*N*-di-*iso*-propylaminoethyl chloride hydrochloride. Reaction with (-)-4-chlorotropic acid (**47**) under usual conditions gave the 2-*N*,*N*-di-*iso*-propylaminoethyl ester (**53**), as a syrup, in low yield (12%). Reaction of **53** with methyl iodide gave the methoiodide salt (**54**) which was converted into the methochloride (**SR 4977**) in 86% yield. Crystallization of the product proved difficult, but gave enough analytically pure material for *in vitro* testing.

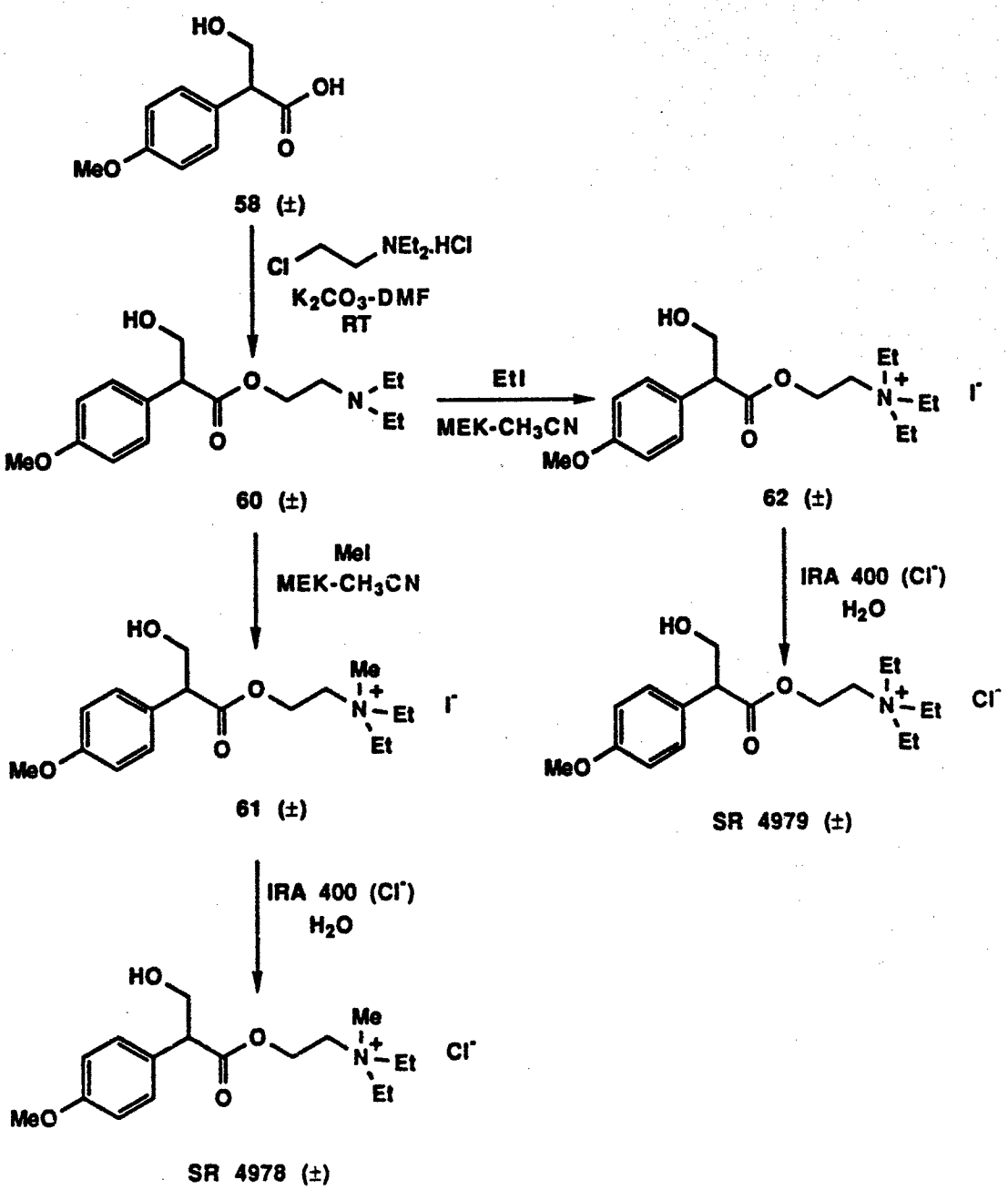


Scheme 14

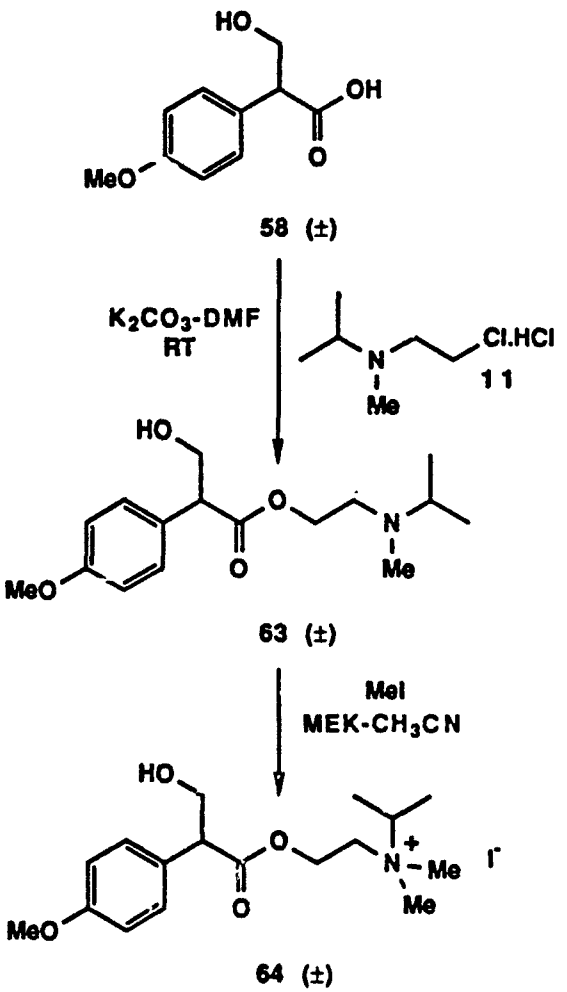
Similar methodology to that used for the synthesis of (±)-4-chlorotropic acid (**46**) has been used to synthesize (±)-4-methoxytropic acid[16] (**58**, Scheme 14). 4'-Methoxybenzeneacetic acid (**55**) was converted into the methyl ester (**56**) by treatment with gaseous HCl in methanol (95%). Reaction with paraformaldehyde in DMSO employing NaOMe as base introduced the hydroxymethyl moiety and cleavage of the ester with NaOH gave (±)-4-methoxytropic acid (**58**) in good overall yield. All attempts at resolution of the racemic mixture have failed to give any pure (-)-4-methoxytropic acid (**59**) primarily because of the insolubility of the parent acid and the lack of differential solubility between the acid and the quinine salts in ethanol-water mixtures usually used for these separations. Many other solvent systems have now been tried in attempts to effect the separation, but without success. Impure (-)-4-methoxytropic acid (**59**) with an $[\alpha]_D$=-9.5° was obtained from water but all efforts at further purification failed.

As a result of this lack of success unresolved (±)-4-methoxytropic acid (**58**) was converted into 2-*N*,*N*-dialkylaminoethyl esters for conversion into quaternary salts. (±)-4-Methoxytropic acid (**58**) on reaction with 2-*N*,*N*-diethylaminoethylchloride hydrochloride under usual conditions gave the 2-*N*,*N*-diethylaminoethyl ester (**60**, Scheme 15). The reaction proceeded sluggishly and even with heating, overall yields were low (20%). Quaternization with methyl iodide and ethyl iodide gave the methoiodide (**61**) and ethoiodide (**62**) respectively which were converted into the chlorides **SR 4978** and **SR 4979** by passage down an IRA 400 (Cl^-) ion exchange resin. Lyophilization gave the two products in analytically pure form. Reaction of (±)-4-methoxytropic acid (**58**) with 2-*N*-*iso*-propyl-*N*-methylaminoethyl chloride hydrochloride (**11**) gave the 2-*N*-*iso*-propyl-*N*-methylaminoethyl ester (**63**) as a clear oil in low yield (Scheme 16). Reaction of **63** with methyl iodide proceeded very slowly and was incomplete after 168h.

Research by Dan Parish (Private Communication 02-1989; Table 3) has shown excellent activity for a series of 2-*N*,*N*-dialkylaminoethyl-1-phenylcyclohexane-1-carboxylates, acting as pretreatment drugs protecting cholinesterase against phosphonylation and therefore poisoning by organophosphorus agents. The similarity in structure between these compounds and many of the esters we have synthesized suggested that we should attempt to introduce a hydroxyl function into the cyclohexane ring portion of the molecule in order to potentiate muscarinic receptor binding and introduce the potential for cleavage by cholinesterase. The endpoint for this modification could be the emergence of a series of drugs which would act both as pretreatment and as anticholinesterase agents.


HO
OH
O
MeO
58 (±)
Cl
NEt2.HCl
K2CO3-DMF
RT
HO
O
O
N
Et
Et
MeO
60 (±)
EtI
MEK-CH3CN
HO
O
O
Et
N+
Et
Et
I-
MeO
62 (±)
MeI
MEK-CH3CN
HO
O
O
Me
N+
Et
Et
I-
MeO
61 (±)
IRA 400 (Cl-)
H2O
HO
O
O
Et
N+
Et
Et
Cl-
MeO
SR 4979 (±)
IRA 400 (Cl-)
H2O
HO
O
O
Me
N+
Et
Et
Cl-
MeO
SR 4978 (±)

Scheme 15

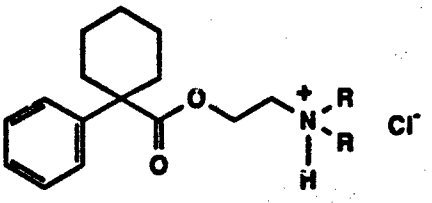


Scheme 16

The synthesis of 2-hydroxy-1-phenylcyclohexylcarboxylic acid, methyl ester (68, Scheme 17) was therefore initiated, for conversion into suitable 2-*N*,*N*-dialkylaminoethyl esters (69). Reaction of the acetal of 5-bromovaleraldehyde with benzeneacetic acid, methyl ester using sodamide in liquid ammonia as base gave the intermediate (66) in 86% yield, which was readily deprotected to the appropriate aldehyde (67). All attempts to synthesize 2-hydroxy-1-phenylcyclohexylcarboxylic acid methyl ester (68) by base-catalysed cyclization of this intermediate aldehyde failed to yield any product. Starting material was consumed in all cases,

Table 3

Intramuscular Pretreatment Survival Efficacy data[a] for
2-*N,N*-Dialkylaminoethyl-1-phenylcyclohexane-1-carboxylates in the Mouse



SRI Code #	AMINE	IM LD_{50} (mmol/kg)	15 min. 1/64	1/16	1/4	60 min. 1/64	1/16	1/4
PRE-078	$N(CH_3)_2$	>0.91	2	0	6	0	0	0
PRE-079	pyrrolidine	>1.04	0	0	6	0	0	4

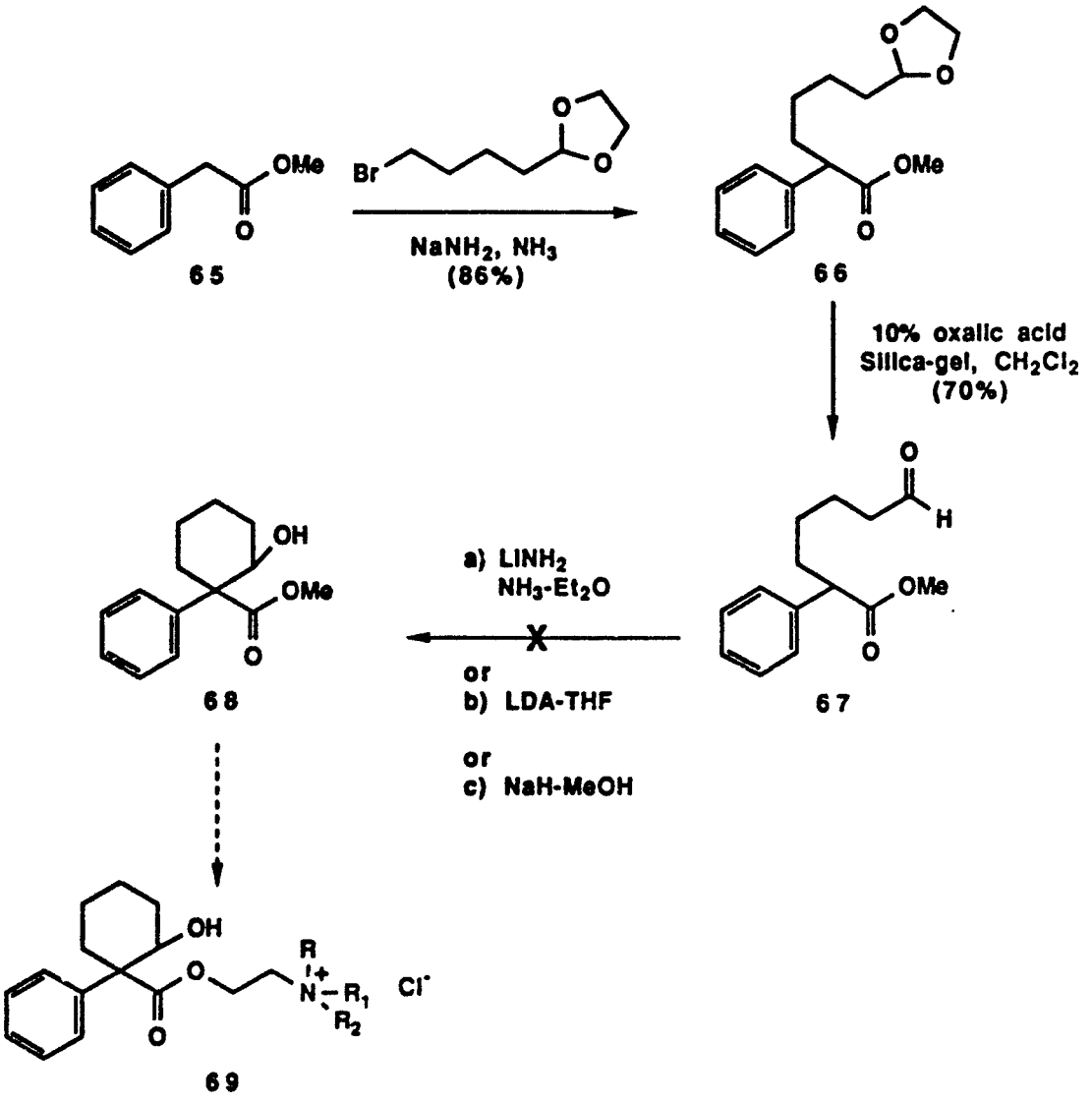
[a] Pretreatment compound administered 15 or 60 minutes prior to GD challenge, at doses equal to the indicated fraction of their LD_{50}. Number of survivors out of 10 is indicated.

Dan Parish. Private Communication 02-89

using a variety of bases and solvents, but the only products isolated appeared to be dimers and trimers presumably formed through Aldol-type condensations of the uncyclized material.

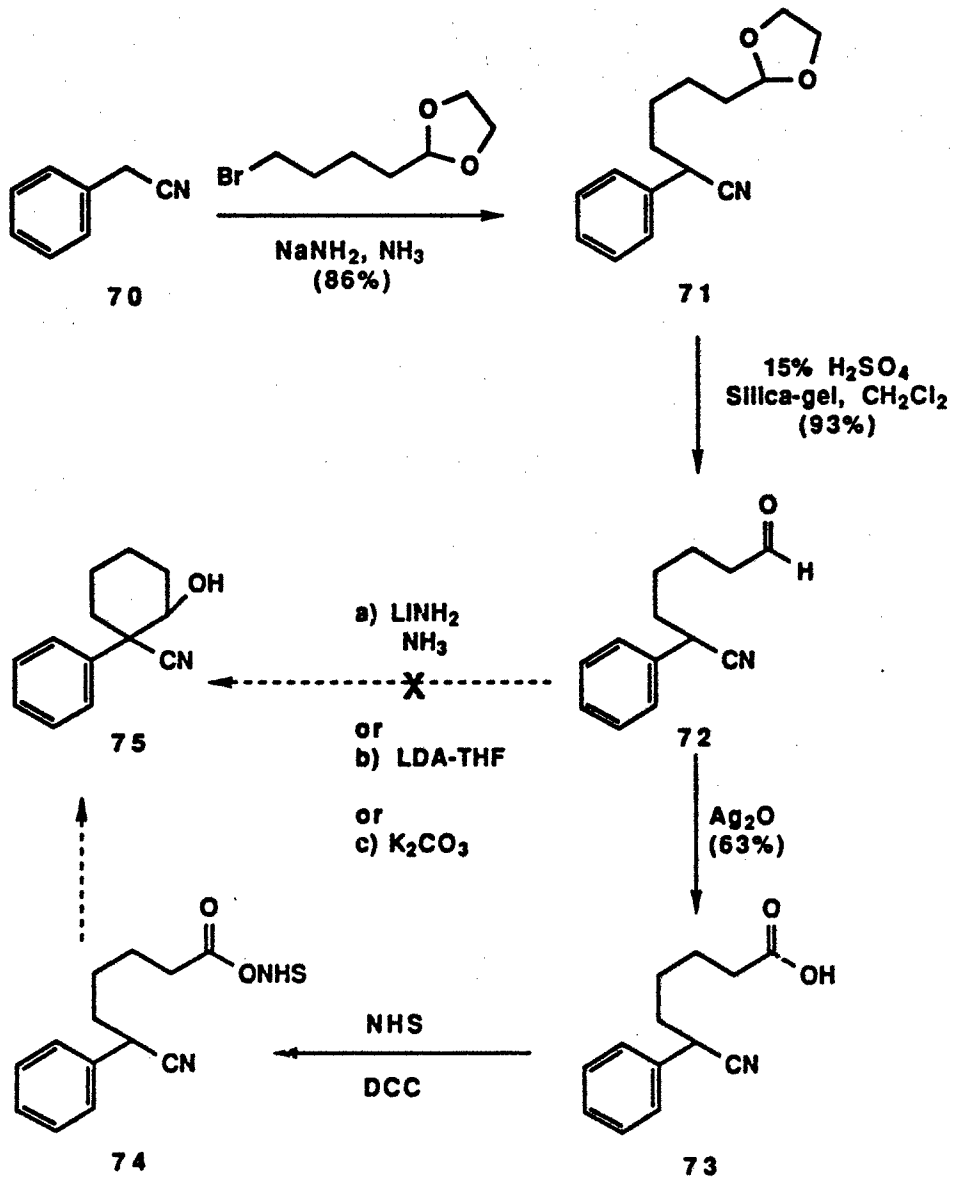
Two unsuccessful approaches to the target molecule via the synthesis of intermediate nitriles and cyclization to 2-hydroxy-1-phenylcyclohexylnitrile (75), were also investigated and are shown in Scheme 18. Base-catalyzed alkylation of benzyl nitrile (70) with 5-bromovaleraldehyde, protected as the acetal, gave the intermediate (71) in high yield. Deprotection to the aldehyde (72) proceeded smoothly but all attempts at base-catalyzed cyclization to (75) proved unsuccessful. Oxidation of the intermediate aldehyde (72), with silver (I) oxide, gave the carboxylic acid (73) which was converted by standard methodology into the NHS ester (74). Base-catalyzed cyclization of this ester also failed to yield any of the desired target and gave a large number of other products. Further investigation of the synthesis of 2-hydroxy-1-phenylcyclohexylcarboxylic acid was therefore discontinued.

All crystalline products described in this report which were shown to be pure by elemental analysis have been tested *in vitro* at SRI International for muscarinic receptor binding affinity and



Scheme 17

rate of hydrolysis by cholinesterase and were sent to USAMRICD for *in vivo* testing as atropine substitutes in the Anticholinergic efficacy screen.


CN
Br
O
O
NaNH2, NH3
(86%)
70
71
15% H2SO4
Silica-gel, CH2Cl2
(93%)
OH
CN
a) LINH2
NH3
or
b) LDA-THF
or
c) K2CO3
75
72
Ag2O
(63%)
ONHS
NHS
DCC
74
73
OH
H

Scheme 18

Biology

In vitro Pharmacology

In vitro testing to determine muscarinic receptor binding affinity and rates of cholinesterase hydrolysis for all optically pure quaternary salts synthesized during this contract period was completed in duplicate (Tables 4-7).

Each compound was tested for binding affinity at the muscarinic receptor, and for rate of hydrolysis, in the presence of serum cholinesterase at physiological levels. Our aim was to develop compounds with high affinity for the muscarinic acetylcholine receptor, and with a range of hydrolysis rates in the presence of serum cholinesterase. With these compounds, and the appropriate *in vivo* testing, we had planned to test our hypothesis, that a hydrolyzable muscarinic antagonist would be a superior antidote to anticholinesterase poisoning.

Binding was conducted on rat brain membranes, as we have described in previous reports. Briefly, membranes were incubated in the presence of [^{3}H] QNB and the appropriate test compound. Incubations lasted two hours at 37°C and then samples were filtered over glass fiber filters. IC_{50} values were determined graphically, and K_i values calculated from the Chang-Prusoff equation:

$$K_i = IC_{50}/1+L/K_d$$

In this equation, L is the radioligand concentration, and K_d is the dissociation constant of the radioligand. We have previously determined that the K_d for [^{3}H] QNB is approximately 0.2 nM.

Hydrolysis rates were determined using a modified radioreceptor assay for each compound. For these experiments, the test compound was incubated at 37°C in brain membranes that had been supplemented with 6 U/ml of serum cholinesterase. The reaction was stopped at various times with 40 μM eserine, at which time [^{3}H] QNB was added to the reaction mixture. The incubation was continued for an additional 2 h, at which time the samples were filtered as previously. This method depends on the ability of the compound to inhibit [^{3}H] QNB binding i.e. that in the presence of the cholinesterase, the test compound will hydrolyze at a particular rate, and thus its ability to inhibit [^{3}H] QNB binding will diminish. By determining the extent of inhibition

after various lengths of incubation with cholinesterase, we can estimate the rate at which the test compounds will be hydrolyzed *in situ.*

The results, shown in Tables 4-7, demonstrate some definite trends. As expected, the affinity of atropine was in the sub-nanomolar range, and that of acetylcholine in the micromolar range. In addition, atropine was not hydrolyzed under the conditions of the experiments, but acetylcholine was rapidly hydrolyzed, so that within 10 minutes it no longer significantly inhibited [^{3}H] QNB binding.

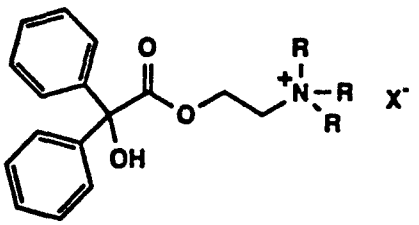
The esters of benzilic acid exhibited binding affinity to the muscarinic receptor somewhat similar to that of atropine, but were cleaved readily by cholinesterase (Table 4). Benactyzine hydrochloride (SR 4958), which has been used as an antidote for organophosphorus poisoning in combination with atropine, bound less strongly in our studies but exhibited a half-life of 60 minutes. This stability falls in the range we suggested would be appropriate for an effective agent.

The *in vitro* results for the 2-*N*,*N*-dialkylaminoethyl esters of S-(-)-tropic acid are extremely promising, and show that several of the compounds synthesized exhibited enhanced muscarinic receptor binding affinity (e.g. SR 4952 and SR 4953), when compared to atropine, and that all the chlorides with the exception of SR 4950 were cleaved by cholinesterase with half-lives in the range of 29-68 minutes (Table 5).

Comparison of the results between Tables 5 and 7 show that the (-)-4-chlorotropic acid derivatives all bind to the muscarinic receptor far more weakly than their tropic acid counterparts and that the binding trends in this series may be less dependent on the onium head group, although the result for SR 4977 may be something of an anomaly. Comparison of the rates of cholinesterase hydrolysis for SR 4976 and SR 4977 with SR 4952 and SR 4953, shows that the (-)-4-chlorotropic acid derivatives are hydrolyzed more readily than their tropic acid counterparts. These results may be explained chemically, by suggesting that the change in rates, are caused by the inductive effect that the chlorine atom has on the rate of hydrolysis of an ester of benzeneacetic acid, even though the carbonyl functionality is one carbon removed from the π ring system. They may also be explained enzymatically by suggesting that the presence of the lipophilic chlorine atom increases the binding of the quaternary salts to the active site in cholinesterase thereby enhancing the rate of hydrolysis, and that in the case of the weaker binding to the muscarinic receptor the effect is reversed. It is probable that both mechanisms play a part.

Table 4

In vitro data for Quaternary salts of 2-*N,N*-dialkylaminoethyl Benzilic acid Esters

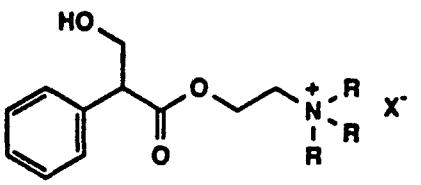


WR. No.	Bottle No.	SR No.	AMINE	Musc. Bind. K_i(nM)	Cholin. Hydrol. t(1/2)min.
268154	BL58134	SR 4956	NEt_2MeCl	0.48	5
268153	BL58143	SR 4957	NEt_3Cl	0.55	25
Unknown	BL58152	SR 4958[a]	$NEt_2.HCl$	0.76	60

[a] Benactyzine HCl

Table 5

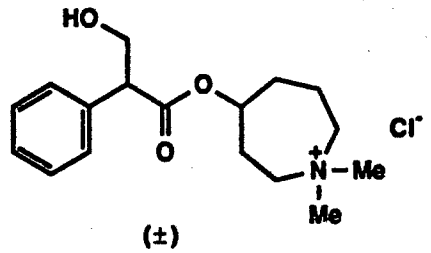
In vitro data for Quaternary salts of 2-*N,N*-Dialkylaminoethyl Tropic acid Esters



WR. No.	Bottle No.	SR No.	AMINE	ISOMER	Musc. Bind K_i(nM)	Cholin. Hydrol. t($^1/_2$)min.
268155	BL58072	SR 4950	NEt_2MeCl	(-)	0.28	NA
251888	BK71525	NA	NEt_2MeI	(-)	1.50	>120
Unknown	BM03581	SR 4974	NEt_2MeCl	(+)	13.20	40
251887	BK71507	SR 4968	NEt_2MeI	(+)	9.10	30
268156	BL58081	SR 4951	$N^iPr_2.HCl$	(-)	0.60	35
268157	BL58090	SR 4952	$NMe_2{}^iPrCl$	(-)	0.07	35
268158	BL58107	SR 4953	N^iPr_2MeCl	(-)	0.16	29
268159	BL58116	SR 4954	PiperidineMeCl	(-)	0.58	68
268160	BL58125	SR 4955	PiperidineEtCl	(-)	0.49	32
Unknown	BL58465	SR 4969	NEt_3Cl	(-)	0.33	NA
		Atropine			0.32	

Table 6

In vitro data for SR 4972

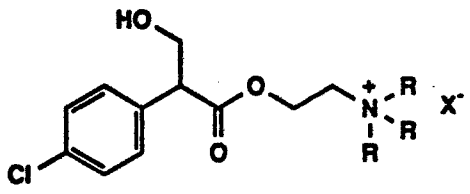


(±)

WR. No.	Bottle No.	SR No.	ISOMER	Musc. Bind K_i(nM)	Cholin. Hydrol. t($^1/_2$)min.
Recently submitted		SR 4972	(±)	2.40	None

Table 7

In vitro data for Quaternary Salts of 2-*N,N*-Dialkylaminoethyl 4-Chlorotropic Acid Esters



WR. No.	Bottle No.	SR No.	AMINE	ISOMER	Musc. Bind K_i(nM)	Cholin. Hydrol. t($^1/_2$)min.
Unknown	BM03572	SR 4973	NEt_2MeCl	(-)	5.70	16
Recently submitted		SR 4975	NEt_3Cl	(-)	5.60	25
Recently submitted		SR 4976	$NMe_2{}^iPrCl$	(-)	2.70	20
Recently submitted		SR 4977	N^iPr_2MeCl	(-)	31.00	20

The K_i value of 13.20 nM for the binding of SR 4974 to the muscarinic receptor compared to that of 0.28 nM for SR 4950 (Table 5) once again clearly emphasizes the binding stereospecificity of the receptor for derivatives of S-(-)-tropic acid. The *in vitro* results for SR 4972 (Table 6) show that the presence of the seven membered onium ring does not enhance binding to the muscarinic receptor and prevents any significant binding to cholinesterase for hydrolysis to occur.

These *in vitro* results demonstrate that we have now synthesized molecules which exhibit the properties we were attempting to introduce into a drug i.e. the ability to bind more strongly than atropine to the muscarinic receptor and to be hydrolyzed into inactive products by serum cholinesterase with half-lives in the range of 30-60 minutes.

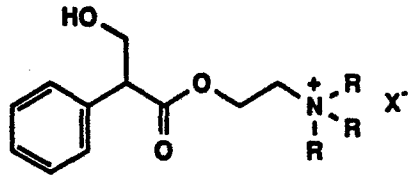
In vivo Testing by USAMRICD

In vivo test results for several of the compounds which were synthesized and submitted to USAMRICD are shown in Tables 8-13. Unfortunately these compounds were tested in both the Pretreatment and Reactivator survival efficacy screens and not in the mode for which they were designed as substitutes for atropine in the appropriate Anticholinergic efficacy screen. This difference in mode of administration makes analysis and comparison of data with that previously obtained impossible.

Results for the compounds tested in these screens were disappointing and yielded very little useful structure-activity information.

Table 8

In vivo Intramuscular Reactivator Survival Efficacy data[a] for 2-*N,N*-Dialkylaminoethyl Tropic Acid Esters Against GD in the Mouse



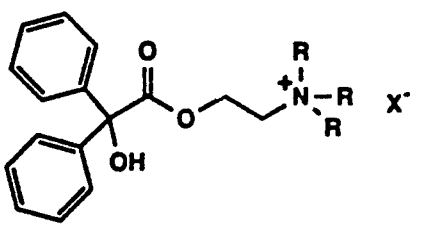
WR. No.	Bottle No.	SR No.	AMINE	ISOMER	IM LD_{50} (mmol/kg)	1/64	1/16	1/4
268155	BL58072	SR 4950	NEt_2MeCl	(-)	0.53	2[b]	3[b]	4[b]
						0	0	0
268156	BL58081	SR 4951	$N^iPr_2.HCl$	(-)	>1.21	0[b]	0[b]	1[b]
						1	1	1
268157	BL58090	SR 4952	$NMe_2{}^iPrCl$	(-)	0.70	0[b]	0[b]	0[b]
						2	0	0
268158	BL58107	SR 4953	N^iPr_2MeCl	(-)	0.24	0[b]	0[b]	3[b]
						0	0	1
268159	BL58116	SR 4954	PiperidineMeCl	(-)	0.58	0[b]	1[b]	0[b]
						0[b]	0[b]	1[b]
						1	0	1
268160	BL58125	SR 4955	PiperidineEtCl	(-)	0.76	0[b]	0[b]	0[b]
						0	0	0
Unknown	BL58465	SR 4969	NEt_3HCl	(-)	-	No Results		

[a] Reactivator compound administered simultaneously with atropine sulfate 10 seconds after GD challenge at doses equal to the indicated fraction of their LD_{50}. Number of survivors out of ten is indicated.

[b] Compounds tested as Reactivators even though cover sheets suggest drugs were tested in the anticholinergic efficacy screen.

Table 9

In vivo Intramuscular Reactivator Survival Efficacy data[a] for 2-*N*,*N*-Dialkylaminoethyl Benzilic Acid Esters Against GD in the Mouse



WR. No.	Bottle No.	SR No.	AMINE	IM LD_{50} (mmol/kg)	1/64	1/16	1/4
268154	BL58134	SR 4956	NEt_2MeCl	1.06	2[b]	3[b]	0[b]
					0	0	1
268153	BL58143	SR 4957	NEt_3Cl	>0.63	2[b]	6[b]	1[b]
					0	1	0
Unknown	BL58182	SR 4958[c]	NEt_2HCl	-	No Results		

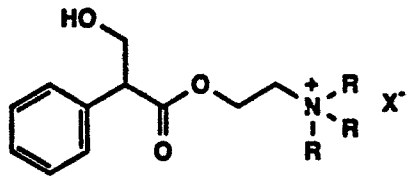
[a] Reactivator compound administered simultaneously with atropine sulfate 10 seconds after GD challenge at doses equal to the indicated fraction of their LD_{50}. Number of survivors out of ten is indicated.

[b] Compounds tested as Reactivators even though cover sheets suggest drugs were tested in the anticholinergic efficacy screen.

[c] Benactyzine.HCl.

Table 10

In vivo Intramuscular Pretreatment Survival Efficacy data[a] for 2-*N*,*N*-Dialkylaminoethyl Tropic Acid Esters Against GD in the Mouse

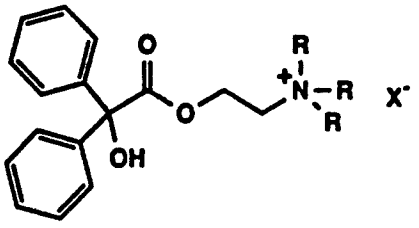


WR. No.	SR No.	AMINE	ISOMER	IM LD_{50} (mmol/kg)	15 min. 1/64	15 min. 1/16	15 min. 1/4	60 min. 1/64	60 min. 1/16	60 min. 1/4
268155	SR 4950	NEt_2MeCl	(-)	0.53	0	0	0	0	1	0
268156	SR 4951	$N^iPr_2.HCl$	(-)	>1.21	1	1	3	2	1	4
268157	SR 4952	$NMe_2{}^iPrCl$	(-)	0.70	0	0	3	0	0	0
268158	SR 4953	N^iPr_2MeCl	(-)	0.24	4	2	3	1	1	1
268159	SR 4954	PiperidineMeCl	(-)	0.58	2	1	2	1	2	2
268160	SR 4955	PiperidineEtCl	(-)	0.76	1	2	5	2	3	2
Unknown	SR 4969	NEt_3Cl	(-)	-	No Results					

[a] Pretreatment compound administered 15 or 60 minutes prior to GD challenge at doses equal to the indicated fraction of their LD_{50} followed by atropine sulfate and 2-PAM intramuscularly 10 seconds after GD challenge. Number of survivors out of 10 is indicated.

Table 11

In vivo Intramuscular Pretreatment Survival Efficacy data[a] for 2-*N,N*-Dialkylaminoethyl Benzilic Acid Esters Against GD in the Mouse

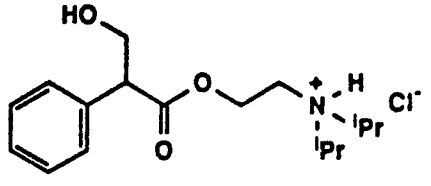


WR. No.	SR No.	AMINE	IM LD_{50} (mmol/kg)	15 min. 1/64	1/16	1/4	60 min. 1/64	1/16	1/4
268154	SR 4956	NEt_2MeCl	1.06	0	1	0	1	0	4
268153	SR 4957	NEt_3Cl	>0.63	0	2	2	1	0	4
Unknown	SR 4958[b]	$NEt_2.HCl$	-			No Results			

[a] Pretreatment compound administered 15 or 60 minutes prior to GD challenge at doses equal to the indicated fraction of their LD_{50} followed by atropine sulfate and 2-PAM intramuscularly 10 seconds after GD challenge. Number of survivors out of 10 is indicated.
[b] Benactyzine.HCl.

Table 12

In vivo Oral Pretreatment Survival Efficacy data[a] for SR 4951 Against GD in the Mouse

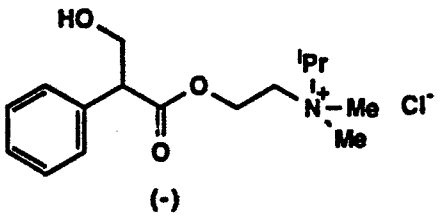


WR. No.	Bottle No.	SR No.	ISOMER	ORAL LD_{50} (mmol/kg)	30 min. 1/64	1/16	1/4	120 min. 1/64	1/16	1/4
268156	BL58081	SR 4951	(-)	>3.03	1	0	2	3	0	0

[a] Pretreatment compound administered by gavage prior to GA challenge at doses equal to the indicated fraction of the LD_{50} followed by atropine sulfate and 2-PAM intramuscularly 10 seconds after GA challenge. Number of survivors out of ten is indicated.

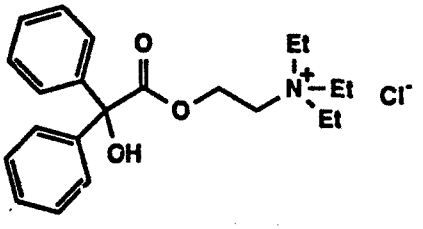
Table 13

In vivo Intramuscular Reactivator Survival Efficacy data[a] for SR 4952 and SR 4957 Against GA in the Mouse



(-)

SR 4952



SR 4957

WR. No.	Bottle No.	SR No.	IM LD_{50} (mmol/kg)	1/64	1/16	1/4
268157	BL58090	SR 4952	0.70	2	1	1
268153	BL58143	SR 4957	>0.63	0	1	0

[a] Reactivator compound administered simultaneously with atropine sulfate 10 seconds after GA challenge at doses equal to the indicated fraction of their LD_{50}. Number of survivors out of ten is indicated.

CONCLUSIONS

During this contract period we have synthesized several quaternary derivatives of 2-*N*,*N*-dialkylaminoalkyl esters of S-(-)-tropic acid and (-)-4-chlorotropic acid that demonstrate muscarinic binding affinities similar to, or in some cases significantly better than atropine and which undergo hydrolytic cleavage by serum cholinesterase *in vitro* at a wide range of differing rates. We have in fact designed compounds that fit our model for agents that would be potentially useful as antidotes for Organophosphorus poisoning.

Unfortunately without the appropriate data from USAMRICD for *in vivo* testing as atropine substitutes in the Anticholinergic efficacy screen we have been unable to determine whether these drugs have any therapeutic value and could be useful as replacements for atropine in humans.

EXPERIMENTAL DETAILS

Melting points were obtained on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. All solvents were purchased as AR grade and where appropriate, were stored over 4Å molecular sieves. All anhydrous reactions were conducted under an atmosphere of argon. Flash chromatography was accomplished using silica gel 60 (230-400 mesh) purchased from EM Science. TLC analyses were performed on glass backed Analtech Uniplates (250 μ, 2 x 8 in).with F-256. Visualization was performed by viewing under ultraviolet light, by exposure to iodine vapor and by charring with H_2SO_4. ^{1}H-NMR analyses were obtained on a Varian XL-400 operating at 400 MHz, or either a JEOL FX90Q or Varian EM 390, both operating at 90 MHz, and were referenced to tetramethylsilane as an internal standard. IR spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. Mass spectra were obtained on a Reibermag Model R10-10C operating in either chemical ionization or desorption-chemical ionization mode. Electron impact mass spectra (EIMS) were obtained on an LKB-9000. Microanalytical data were obtained from Desert Analytics (Tuscon, AZ). Optical rotations were measured on a Perkin-Elmer 141 automatic polarimeter. Reverse phase HPLC was performed on a Spectra-Physics SP8100 liquid chromatograph with an SP8440 UV/Vis detector and a Brownlee Labs "phenyl" reverse phase column.

R-(+)-Tropic Acid Quinine Salt. To a solution of 200 g (0.616 mol) of quinine in 1 L (abs) EtOH was added 102 g (0.614 mol) of (±)-tropic acid in 1 L EtOH. A white solid formed to a solid mass within 1 h. The mixture was allowed to stand at RT for 18 h, filtered, and washed with 50 mL abs EtOH. The solid was recrystallized 3 times from 3.5 L of refluxing EtOH to give 120 g (40%) of R-(+)-tropic acid quinine salt, mp 190.5-192 °C.

S-(-)-Tropic Acid Ephedrine Salt. The filtrate from the above reaction was evaporated to dryness and partitioned between 1 L H_2SO_4 and 1 L diethyl ether. After stirring for 0.5 h, the ether layer was separated and the aqueous layer washed with ether (2 x 1L). The combined ether fractions were washed with satd NaCl solution, dried over $MgSO_4$, filtered and evaporated to give 38 g. This was taken up in 50 mL of 60% EtOH and added to a hot solution of 38 g (0.229 mol) of l-(-)-ephedrine in 50 mL of 60% EtOH. The product which crystallized upon standing overnight was collected by filtration and recrystallized twice from refluxing 60% EtOH (100 mL) to give 39 g (52%) of S-(-)-tropic acid ephedrine salt, mp 127-129 °C.

R-(+)-Tropic Acid. In a large flask, 29.5 g (60.1 mmol) of R-(+)-tropic acid quinine salt was stirred with a mixture of 500 mL of 1 N H_2SO_4 and 500 mL of diethyl ether for 0.5 h. The ether was separated and the aqueous layer extracted with more ether (2 x 300 mL). The combined ether layer was washed with 500 mL of satd NaCl solution, dried over $MgSO_4$, filtered and evaporated to give 7 g (70%) of R-(+)-tropic acid, mp 127-129 °C. $[\alpha]_D = 69.6°$ (2% in 95% EtOH.).

S-(-)-Tropic Acid. In a large flask, 39 g (0.118 mol) of S-(-)-tropic acid ephedrine salt was stirred with a mixture of 750 mL of 1 N H_2SO_4 and 500 mL of diethyl ether for 0.5 h. The ether was separated and the aqueous layer extracted with ethyl acetate (3 x 250 mL). The combined organic fractions were washed with 500 mL of satd NaCl solution, dried over $MgSO_4$, filtered and evaporated to give 18.5 g (94%) of S-(-)-tropic acid, mp 128-129 °C. $[\alpha]_D = -72.6°$ (2% in 95% EtOH).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester (5). To 4.50 g (27.1 mmol) of S-(-)-tropic acid in 150 mL dry DMF under argon was added 5.0 g (36 mmol) of powdered K_2CO_3. The cloudy mixture was stirred at RT for 0.5 h, followed by the addition of 4.8 g (28 mmol) of 2-*N*,*N*-diethylaminoethyl chloride hydrochloride. The mixture was stirred at RT for 40 h, then poured into 500 mL of ice water and extracted with diethyl ether (3 x 250 mL). The ether layer was washed with 250 mL satd NaCl solution, dried over Na_2SO_4, filtered and evaporated to give 5.5 g (77%) of **5** as an oil, R_f=0.25 (95% CH_2Cl_2/5% (MeOH/NH_4OH[95:5]). ^{1}H-NMR ($CDCl_3$) δ 7.31 (s, 5H, aromatic), 4.51-3.72 (m, 5H, $CHCH_2OH$, OCH_2), 2.75 (t, 2H, CH_2N), 2.56 (q, 4H, $N[CH_2Me]_2$), 1.02 (t, 6H, $N[CH_2CH_3]_2$). $[\alpha]_D$=-25° (1.38% in 95% EtOH.).

R-(+)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester (7). Prepared from R-(+)-tropic acid (83 mg, 0.50 mmol) by the same method as **5** to give 100 mg (75%) of **7** as an oil, R_f=0.25 (95% CH_2Cl_2/5% (MeOH/NH_4OH[95:5]). ^{1}H-NMR ($CDCl_3$) same as in **5**.

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester Methoiodide (6). To 3.0 g (11 mmol) of **5** in 20 mL of 2-butanone and 5 mL CH_3CN was slowly added 3 mL of CH_3I (48 mmol). The reaction, kept under argon and protected from light, was stirred at RT for 48 h, then chilled at -4 °C for 24 h to give a white solid. This was filtered to give 2.4 g (54%) of **6**, mp 85-87 °C. $[\alpha]_D$=-17.5° (1.2% in 95% EtOH.) ^{1}H-NMR ($CDCl_3$) δ 7.31 (s, 5H, aromatic), 5.05 (m, 1H, OH), 4.47 (br t, 2H, CO_2CH_2), 3.5-4.1 (m, 3H,

$CHCH_2OH$), 3.27 (q & t, 6H, $CH_2N[CH_2CH_3]_2$), 2.91 (s, 3H, NCH_3), 1.15 (t, 6H, $N[CH_2CH_3]_2$).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester Methochloride (SR 4950). A solution of 2.4 g (5.89 mmol) of **6** in 10 mL of H_2O was passed down an IRA 400 (Cl-) ion exchange resin column and the product was eluted with 150 mL of H_2O. The solvent was removed by lyophilization to give 1.90 g of a foamy solid which was recrystallized from 2-butanone/iPrOH (40/5 mL) at -5 °C to give 1.46 g (78%) of SR 4950, mp 110-112 °C. $[\alpha]_D$=-21 ° (1.32% in 95% EtOH.) ^{1}H-NMR ($CDCl_3$) δ 7.30 (s, 5H, aromatic), 5.4 (m, 1H, OH), 4.46 (br t, 2H, CO_2CH_2), 3.1-4.1 (m, 5H, $CHCH_2OH$, CH_2N), 3.33 (q, 4H, $N[CH_2CH_3]_2$), 2.95 (s, 3H, NCH_3), 1.14 (t, 6H, $N[CH_2CH_3]_2$). Anal calcd for $C_{16}H_{26}ClNO_3$: C, 60.85; H, 8.30; N, 4.43; Cl, 11.22. Found: C, 60.82; H, 8.51; N, 4.40; Cl, 11.21.

R-(+)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester Methoiodide (SR 4968). Prepared from **7** (4.5 g, 16.9 mmol) by the same method as **6** to give 5.6 g (81%) of SR 4968 as a pale yellow oil, mp 85-87 °C. $[\alpha]_D$=16.5 ° (2.5% in 95% EtOH.) ^{1}H-NMR (CD_3CN) δ 7.33 (s, 5H, aromatic), 4.44 (m, 2H, CH_2N), 4.2-3.6 (m, 6H, $CHCH_2OH$, CO_2CH_2), 3.26 (q, 4H, NCH_2Me), 2.88 (s, 3H, NCH_3), 1.19 (t, 6H, NCH_2CH_3).

R-(+)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester Methochloride (SR 4974). Prepared from SR 4968 (5.50 g, 13.5 mmol) by the same method as SR 4950 to give 4.0 g (94%) of SR 4974, mp 109.5-112 °C. $[\alpha]_D$=21.4 ° (2.57% in 95% EtOH.) 400 MHz ^{1}H-NMR (CD_3CN) δ 7.34 (m, 5H, aromatic), 4.56-4.48 (br ddd, 1H, CO_2CH_2), 4.48-4.40 (br ddd, 1H, CO_2CH_2), 3.62 (m, 2H, CH_2N), 4.04 (ddd, 1H, $CHCH_2OH$), 3.91 (ddd, 1H, $CHCH_2OH$), 3.73 (quint, 1H, $CHCH_2OH$), 2.3-2.4 (br, 1H, OH), 3.36 (q, 4H, NCH_2Me), 2.97 (s, 3H, NCH_3), 1.23 (t, 6H, J=7.3 Hz, NCH_2CH_3). Anal calcd for $C_{16}H_{26}ClNO_3$: C, 60.84; H, 8.30; N, 4.43; Cl, 11.23. Found: C, 60.64; H, 8.26; N, 4.40; Cl, 10.98.

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester Ethoiodide (8). Prepared from **5** (3.2 g, 12 mmol) and ethyl iodide in the same manner as **6** to give 4.8 g (93%) of **8** as a syrup. ^{1}H-NMR ($CDCl_3$-CD_3OD) δ 7.30 (s, 5H, aromatic), 4.53 (t, 2H, CO_2CH_2), 4.5-3 5 (m, 3H, $CHCH_2OH$), 3.31 (q, 2H, CH_2CH_3), 2.57 (q, 4H, CH_2CH_3), 1.25 (t, 3H, CH3), 1.02 (t, 6H, CH_3).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester Ethochloride (SR 4969). Prepared from **8** (2.4 g, 5.64 mmol) in the same manner as **SR 4950** to give 1.65 g (88%) of **SR 4969**, mp 112-115 °C. $[\alpha]_D$=-19.2 ° (2.17% in 95% EtOH.) ^{1}H-NMR (DMSO-d_6) δ 7.30 (s, 5H, aromatic), 5.29 (t, 1H, OH), 4.43 (br t, 2H, CO_2CH_2), 3.2-4.1 (m, 5H, $CHCH_2OH$, CH_2N), 3.26 (q, 6H, $N[CH_2Me]_3$), 1.12 (t, 9H, CH_3). Anal calcd for $C_{17}H_{28}ClNO_3$: C, 61.90; H, 8.56; N, 4.25; Cl, 10.75. Found: C, 61.79; H, 8.79; N, 4.39 Cl, 10.74.

2-(*N-Iso*-propyl-*N*-methylamino)ethanol (10). In a flask was combined 20 g (0.266 mol) of 2-(methylamino)ethanol (**9**), 40 g (0.34 mol) of 2-bromopropane and 40 g of K_2CO_3 in 100 mL of 2-butanone. The mixture was heated at reflux for 2 days, then cooled and filtered. The filtrate was evaporated and the residue triturated with 500 mL of diethyl ether and filtered. The filtrate was evaporated to give 26 g (84%) of **10** as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ 3.55 (t, 2H, $HOCH_2$), 2.85 (5, 1H, $CHMe_2$), 2.53 (t, 2H, CH_2N), 2.20 (s, 3H, NCH_3), 1.01 (d, 6H, $CH[CH_3]_2$).

2-(*N-Iso*-propyl-*N*-methylamino)ethyl Chloride Hydrochloride (11). To 25 g (0.21 mol) of **10** in 400 mL of dichloromethane under argon in an ice bath was added 26 mL of $SOCl_2$ in a dropwise manner. The solution was stirred at RT overnight, then reduced to ~100 mL and poured into 500 mL of diethyl ether. The resulting mixture was chilled at -5 °C overnight and the red-brown solid was filtered under argon and washed with ether to give 16 g (44%) of **11**. ^{1}H-NMR (DMSO-d_6) δ 3.58 (t, 2H, $ClCH_2$), 3.2-2.8 (m, 3H, CH_2NCH), 2.18 (d, 3H, NCH_3), 0.78 (d, 3H, $CH[CH_3]_2$), 0.73 (d, 3H, $CH[CH_3]_2$).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N-Iso*-propyl-*N*-methylamino)-ethyl Ester (12). S-(-)-Tropic acid (5.0 g, 30.2 mmol) was treated with **11** (5.8 g, 33.6 mmol) in the same manner as in **5** to give 7.2 g of an oil which was chromatographed on silica gel (98% CH_2Cl_2/2% [MeOH/NH_4OH [95/5]]) to give 6.1 g (77%) of **12**, crystallized from cyclohexane/pentane, mp 35-37 °C. $[\alpha]_D$ = -25.2 ° (2.31 % in 95% EtOH). ^{1}H-NMR ($CDCl_3$) δ 7.31 (s, 5H, aromatic), 4.6-3.7 (, m, 5H, CH_2OH, CO_2CH_2, NCH), 2.87 (t, 2H, $CHCH_2OH$), 2.65 (t, 2H, CH_2N), 1.00 (d, 6H, $CH[CH_3]_2$).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N-Iso*-propyl-*N*-methylamino)-ethyl Ester Methoiodide (13). Prepared from **12** (4.0 g, 15.1 mmol) by the same method as **6**. Recrystallization from MEK/iPrOH gave 4.5 g (73%) of **13**. $[\alpha]_D$ = -15.8 ° (2.66 % in 95%

EtOH). ^{1}H-NMR (DMSO-d_6) δ 7.31 (s, 5H, aromatic), 5.07 (t, 1H, OH), 4.49 (br t, 2H, CO_2CH_2), 3.94 (q, 1H, NCH), 3.80 (m, 3H, CHCH$_2$OH), 3.59 (t, 2H, CH$_2$N), 2.93 (s, 3H, NCH$_3$), 1.23 (d, 6H, CH[CH$_3$]$_2$).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N-Iso*-propyl-*N*-methylamino)-ethyl Ester Methochloride (SR 4952). Prepared from **13** (4.2 g, 10.3 mmol) by the same method as **SR 4950** to give 1.6 g (49%) of **SR 4952**, mp 118-120 °C. $[\alpha]_D$ = -21.1 ° (2.50 % in 95% EtOH). ^{1}H-NMR (DMSO-d_6) δ 7.32 (s, 5H, aromatic), 5.18 (t, 1H, OH), 4.50 (br t, 2H, CO_2CH_2), 4.1-3.5 (m, 4H, CHCH$_2$OH, NCH), 3.62 (br t, 2H, CH$_2$N), 2.94 (s, 3H, NCH$_3$), 1.24 (d, 6H, CH[CH$_3$]$_2$). Anal calcd for $C_{16}H_{26}ClNO_3$•1/2H_2O: C, 59.71; H, 8.35; N, 4.35; Cl, 11.01. Found: C, 59.73; H, 8.27; N, 4.28; Cl, 10.70.

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N-Iso*-propyl-*N*-methylamino)-ethyl Ester Hydrochloride (14). To 3.0 g (11.3 mmol) of **12** in 100 mL of ether was added ethereal HCl until no more solid precipitated. The mixture was evaporated to an oil, which was taken up in iPrOH and MEK added until the solution began to cloud. The mixture was placed in the freezer to give a precipitate which melted as the temp was warmed to 0 °C. Repeated attempts to recrystallize the material have been unsuccessful. Evaporation of the solvent gave 3.2 g (94%) of **14** as a pair of diastereomeric salts. 400 MHz ^{1}H-NMR ($CDCl_3$) δ 7.32 (d, 5H, aromatic), 4.45 (m, 3H, CO_2CH_2, OH), 3.96 (dd, 1H, CHCH$_2$OH), 3.84 (ddd, 1H, CHCH$_2$OH), 3.63 (ddd, 1H, CHCH$_2$OH), 3.42 (m, 2H, CH$_2$N), 3.21 (m, 1H, NCH), 2.58 (d, NCH$_3$), 2.57 (d, NCH$_3$), 1.23 (d, CHCH$_3$), 1.21 (d, CHCH$_3$), 1.16 (d, CHCH$_3$), 1.15 (d, CHCH$_3$).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N,N*-Di-*iso*-propylamino)ethyl Ester (15). Prepared from S-(-)-Tropic acid (6.7 g, 40.3 mmol) and 2-di-*N,N-iso*-propylaminoethyl chloride hydrochloride (8.9 g, 44.5 mmol) by the same method as **5** to give 10 g of an oil. This was chromatographed on silica gel (98% CH_2Cl_2/2% [MeOH/NH_4OH [95/5]]) to give 8 g (68%) of **15** as a syrup. $[\alpha]_D$ = -30 ° (2.68 % in 95% EtOH). ^{1}H-NMR ($CDCl_3$) δ 7.62 (s, 5H, aromatic), 4.43 (t, 2H, CO_2CH_2), 4.6-4.0 (m, 3H, CHCH$_2$OH), 3.31 (sept, 1H, CHMe$_2$), 2.96 (t, CH$_2$N), 1.31 (d, 6H, CH[CH$_3$]$_2$).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N,N*-Di-*iso*-propylamino)ethyl Ester Methoiodide (16). Prepared from **15** (4.0 g, 13.6 mmol) by the same method as **6**. Recrystallization from MEK/iPrOH gave 4.5 g (76%) of **16**. $[\alpha]_D$ = -16.7 ° (2.50 % in 95% EtOH). ^{1}H-NMR (DMSO-d_6) δ 7.32 (s, 5H, aromatic), 5.18 (t, 1H, OH), 4.44 (t, 2H,

CO_2CH_2), 4.1-3.5 (m, 4H, $CHCH_2OH$, NCH), 3.55 (q, 2H, CH_2N), 2.80 (s, 3H, NCH_3), 1.28 (d, 6H, $CH[CH_3]_2$).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N,N*-Di-*iso*-propylamino)ethyl Ester Methochloride (SR 4953). Prepared from **16** (4.50 g, 10.3 mmol) by the same method as **SR 4950** to give 3.4 g (95%) of **SR 4953**, mp 111-113.5 °C. $[\alpha]_D$ = -20.6 ° (2.50 % in 95% EtOH). ^{1}H-NMR (DMSO-d_6) δ 7.32 (s, 5H, aromatic), 5.18 (t, 1H, OH), 4.45 (t, 2H, CO_2CH_2), 4.2-3.7 (m, 4H, $CHCH_2OH$, NCH), 3.56 (q, 2H, CH_2N), 2.81 (s, 3H, NCH_3), 1.25 (d, 6H, $CH[CH_3]_2$). Anal calcd for $C_{18}H_{30}ClNO_3$: C, 62.87; H, 8.79; N, 4.07; Cl, 10.31. Found: C, 63.10; H, 9.00; N, 3.94; Cl, 10.12.

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(*N,N*-Di-*iso*-propylamino)ethyl Ester Hydrochloride (SR 4951). To 3.0 g (10.2 mmol) of **15** in 100 mL of diethyl ether under argon at 0 °C was added ethereal HCl until no more solid was formed. Filtration of the solid gave 1.9 g (50%) of **SR 4951**, mp 91-94 °C. $[\alpha]_D$ = -15.9 ° (2.38% in 95% EtOH). ^{1}H-NMR (DMSO-d_6) δ 7.30 (s, 5H, aromatic), 5.10 (t, 1H, OH), 4.41 (t, 2H, CO_2CH_2), 4.1-3.4 (m, 4H, $CHCH_2OH$, NCH), 3.36 (q, 2H, CH_2N), 1.27 (dd, 6H, $CH[CH_3]_2$). Anal calcd for $C_{17}H_{28}ClNO_3$: C, 61.90; H, 8.56; N, 4.25; Cl, 10.76. Found: C, 61.68; H, 8.62; N, 4.18; Cl, 10.52.

S-(-)-α-Hydroxymethyl)benzeneacetic Acid, 2-(Pyrrolidin-1-yl)ethyl Ester (17). Prepared from S-(-)-tropic acid (4.00 g, 24.1 mmol) and 1-(2-chloroethyl)pyrrolidine hydrochloride (4.1 g, 24.1 mmol) by the same method as **5** to give 4.3 g of a brown oil. This was chromatographed on a silica gel column eluting with CH_2Cl_2, followed by 3% MeOH/NH_4OH[95/5] in CH_2Cl_2, then 5% MeOH/NH_4OH[95/5] in CH_2Cl_2 to give 2.84 g (45%) of **17** as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 7.20 (s, 5H, aromatic), 4.40 (q, 2H, $CHCH_2OH$), 4.1-3.6 (m, 4H, CO_2CH_2, $CHCH_2OH$), 2.70 (t, 2H, CH_2N), 2.4-2.6 (m, 4H, NCH_2), 1.8-1.6 (m, 4H, CH_2CH_2).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(Piperidin-1-yl)ethyl Ester (18). S-(-)-Tropic acid (7.00 g, 42.1 mmol) was treated with 8.5 g (46.1 mmol) of 1-(2-chloroethyl)piperidine hydrochloride in the same manner as in **5** to give 10.6 (91%) of **18** as a low melting solid. $[\alpha]_D$ = -21.1 ° (2.64% in 95% EtOH). ^{1}H-NMR ($CDCl_3$) δ 7.31 (s, 5H, aromatic), 3.5-4.5 (br m, 5H, $CHCH_2OH$, CO_2CH_2), 2.9 (q, 2H, CH_2N), 2.2-2.7 (m, 4H, NCH_3) and 1.3-1.8 (m, 6H, ring CH_2s).

S-(-)-α-Hydroxymethyl)benzeneacetic Acid, 2-(Pyrrolidin-1yl)ethyl Ester Methoiodide (19). Prepared from **17** (3.48 g, 13.22 mmol) by the same method as **6** to give 5.41 g (100%) of **19** as a brown oil. The material resisted crystallization and was not purified or characterized further.

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(Piperidin-1-yl)ethyl Ester Methoiodide (20). Prepared from **18** (4.6 g, 16.0 mmol) by the same method as in **6** to give 6.66 g (96%) of **20**, mp 119-122 °C. $[\alpha]_D$ = -15.7 ° (2.67% in 95% EtOH). ^{1}H-NMR (DMSO-d_6) δ 7.31 (s, 5H, aromatic), 5.04 (t, 1H, O<u>H</u>), 4.49 (br t, 2H, $CO_2C\underline{H}_2$), 4.1-3.5 (m, 3H, $C\underline{H}C\underline{H}_2OH$), 3.30 (br t, 2H, $C\underline{H}_2N$), 3.00 (s, 3H, $NC\underline{H}_3$), 1.8-1.3 (m, 10H, ring $C\underline{H}_2$s).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(Piperid-1-yl)ethyl Ester Methochloride (SR 4954). Prepared from **20** (4.5 g, 10.7 mmol) by the same method as **SR 4950** to give 3.2 g (91%) of **SR 4954**, mp 126-127.5 °C. $[\alpha]_D$ = -22.6 ° (2.53% in 95% EtOH). ^{1}H-NMR (DMSO-d_6) δ 7.31 (s, 5H, aromatic), 5.24 (t, 1H, O<u>H</u>), 4.50 (br t, 2H, $CO_2C\underline{H}_2$), 4.1-3.55 (m, 3H, $C\underline{H}C\underline{H}_2OH$), 3.75 (br t, 2H, $C\underline{H}_2N$), 3.02 (s, 3H, $NC\underline{H}_3$), 3.3-3.95 (m, 10H, ring $C\underline{H}_2$s). Anal calcd for $C_{17}H_{26}ClNO_3$: C, 62.28; H, 7.99; N, 4.27; Cl, 10.81. Found: C, 62.54; H, 8.09; N, 4.08; Cl, 10.88.

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(Piperidin-1-yl)ethyl Ester Ethoiodide (21). Prepared from **18** (5.0 g, 18.0 mmol) and EtI by the same method as **6** to give 7.3 g (94%) of **21**, mp 123-125 °C. $[\alpha]_D$ = -14.7 ° (2.53% in 95% EtOH). ^{1}H-NMR ($CDCl_3$-CD_3OD) δ 7.32 (s, 5H, aromatic), 4.55 (t, 2H, $CO_2C\underline{H}_2$), 4.11 (q, 2H, $NC\underline{H}_2Me$), 4.0-3.5 (m, 3H, $C\underline{H}C\underline{H}_2OH$), 3.40 (br t, 2H, $C\underline{H}_2N$), 1.76 (br s, 10H, ring $C\underline{H}_2$s), 1.25 (t, 3H, $C\underline{H}_3$).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(Piperidin-1-yl)ethyl Ester Ethochloride (SR 4955). Prepared from **21** (5.0 g, 11.5 mmol) by the same method as **SR 4950** to give 3.8 g (76%) of **SR 4955**, mp 109-111 °C. $[\alpha]_D$ = -17.4 ° (1.91% in 95% EtOH). ^{1}H-NMR (DMSO-d_6) δ 7.31 (s, 5H, aromatic), 5.19 (t, 1H, O<u>H</u>), 4.44 (br t, 2H, $CO_2C\underline{H}_2$), 4.1-3.2 (m, 7H, $C\underline{H}C\underline{H}_2OH$, $C\underline{H}_2NC\underline{H}_2Me$), 1.3-1.95 (br s, 10H, ring $C\underline{H}_2$s), 1.11 (t, 3H, $C\underline{H}_3$). Anal calcd for $C_{18}H_{28}ClNO_3$: C, 63.24; H, 8.26; N, 4.10; Cl, 10.37. Found: C, 63.36; H, 8.35; N, 4.02; Cl, 10.36.

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 2-(Pyrrolidin-1-yl)ethyl Ester Hydro-chloride (23). Prepared from **17** (2.75 g, 10.45 mmol) and ethereal HCl by the same method as **SR 4951**. Recrystallization from EtOH/Et_2O gave 2.81 g (90%) of **23**. Anal calcd for $C_{15}H_{22}ClNO_3$: C, 60.10; H, 7.40; N, 4.67; Cl, 11.87. Found: C, 60.13; H, 7.47; N, 4.71; Cl, 11.60.

2,2-Diphenyl-2-hydroxyacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester (24). Treatment of benzilic acid (16.0 g, 17.0 mmol) and 2-*N,N*-diethylaminoethyl chloride hydrochloride (12.5 g, 72.6 mmol) by the same method as **5** gave 20 g (87%) of **24**. ^{1}H-NMR ($CDCl_3$) δ 7.41 (m, 10H, aromatic), 4.31 (t, 2H, $CO_2C\underline{H}_2$), 2.66 (t, 2H, $C\underline{H}_2N$), 2.46(q, 4H, $C\underline{H}_2Me$), 0.93 (t, 6H, $C\underline{H}_3$).

2,2-Diphenyl-2-hydroxyacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester Hydro-chloride (SR 4958). Prepared from **24** (5.0 g, 15.3 mmol) by the same method as **SR 4951** to give 5.2 g (93%) of **SR 4958**, mp 176.5-178 °C. ^{1}H-NMR (DMSO-d_6) δ 7.31 (s, 10H, aromatic), 6.85 (s, 1H, O<u>H</u>), 4.52 (br t, 2H, $CO_2C\underline{H}_2$), 3.33 (br t, 2H, $C\underline{H}_2N$), 2.29 (q, 4H, $C\underline{H}_2Me$), 1.07 (t, 6H, $C\underline{H}_3$). Anal calcd for $C_{20}H_{26}ClNO_3$: C, 66.01; H, 7.20; N, 3.85; Cl, 9.74. Found: C, 65.74; H, 7.31; N, 3.87; Cl, 9.91.

2,2-Diphenyl-2-hydroxyacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester Metho-iodide. Prepared from **24** (5.0 g, 15.3 mmol) by the same method as **6** to give 6.0 g (84%) of product, mp 139-141 °C. ^{1}H-NMR (DMSO-d_6) δ 7.34 (s, 10H, aromatic), 6.75 (s, 1H, O<u>H</u>), 4.57 (br t, 2H, $CO_2C\underline{H}_2$), 3.58 (br t, 2H, $C\underline{H}_2N$), 3.20 (q, 4H, $C\underline{H}_2Me$), 2.82 (s, 3H, $C\underline{H}_3$), 1.05 (t, 6H, $C\underline{H}_3$).

2,2-Diphenyl-2-hydroxyacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester Ethoiodide. Prepared from **24** (5.0 g, 15.3 mmol) and EtI (6 mL, 74 mmol) by the same method as **6** to give 6.1 g (83%) of product, mp 163-165 °C. ^{1}H-NMR (DMSO-d_6) δ 7.34 (s, 10H, aromatic), 6.75 (s, 1H, O<u>H</u>), 4.54 (br t, 2H, $CO_2C\underline{H}_2$), 3.53 (br t, 2H, $C\underline{H}_2N$), 3.17 (q, 4H, $C\underline{H}_2Me$), 1.01 (t, 6H, $C\underline{H}_3$).

2,2-Diphenyl-2-hydroxyacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester Metho-chloride (SR 4956). Prepared from the methoiodide (5.0 g, 10.6 mmol) by the same method as **SR 4950** to give 3.45 g (86%) of **SR 4956**, mp 202-204 °C. ^{1}H-NMR (DMSO-d_6) δ 7.34 (s, 10H, aromatic), 6.84 (s, 1H, O<u>H</u>), 4.55 (br t, 2H, $CO_2C\underline{H}_2$), 3.60 (br t, 2H, $C\underline{H}_2N$), 3.22

(q, 4H, $C\underline{H}_2Me$), 1.06 (t, 6H, $C\underline{H}_3$). Anal calcd for $C_{21}H_{28}ClNO_3$: C, 66.74; H, 7.47; N, 3.71; Cl, 9.32. Found: C, 66.80; H, 7.58; N, 3.62; Cl, 9.33.

2,2-Diphenyl-2-hydroxyacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester Ethochloride (SR 4957). Prepared from the ethoiodide (5.0 g, 10.3 mmol) by the same method as **SR 4950** to give 3.7 g (92%) of **SR 4957**, mp 232-233 °C dec. ^{1}H-NMR (DMSO-d_6) δ 7.34 (s, 10H, aromatic), 6.82 (s, 1H, O$\underline{H}$), 4.53 (br t, 2H, $CO_2C\underline{H}_2$), 3.55 (br t, 2H, $C\underline{H}_2N$), 3.18 (q, 4H, $C\underline{H}_2Me$), 1.02 (t, 6H, $C\underline{H}_3$). Anal calcd for $C_{22}H_{30}ClNO_3$: C, 67.42; H, 7.71; N, 3.57; Cl, 9.05. Found: C, 67.48; H, 7.78; N, 3.51; Cl, 9.16.

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 1-Methylpyrrolidin-2-ylethyl Ester (25) and S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 1-methylhexahydro-1H-azepin-4-yl Ester (26). S-(-)-Tropic acid (5.00 g, 30.1 mmol) was treated with 2-(2-chloroethyl)-1-methylpyrrolidine hydrochloride in the same manner as **5** for 7 days. Chromatography (2x) on silica gel (95% CH_2Cl_2/5%[MeOH/NH_4OH(95/5)]) gave 0.95 g of **25** and 2.4 g of **26**. **25**: MS m/e 277. ^{1}H-NMR ($CDCl_3$) δ 7.28 (s, 5H, aromatic), 4.3-3.6 (m, 5H, C$\underline{H}C\underline{H}_2OH$, O$C\underline{H}_2$), 3.0 (m, 1H, C$\underline{H}$N), 2.21 (s, 3H, N$C\underline{H}_3$), 2.4-1.3 (br, 6H, ring $C\underline{H}_2$). **26**: MS m/e 277. ^{1}H-NMR ($CDCl_3$) δ 7.27 (s, 5H, aromatic), 5.05 (m, 1H, OC$\underline{H}$), 4.3-3.6 (m, 4H, C$\underline{H}C\underline{H}_2O\underline{H}$), 2.5 (m, 4H, $C\underline{H}_2N$), 2.1-1.5 (m, 6H, ring $C\underline{H}_2$), 2.3 (s, 3H, N$C\underline{H}_3$).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 1-Methylpyrrolidin-2-ylethyl Ester Methoiodide (27). Prepared from **25** (0.95 g, 3.42 mmol) by the same method as **6**. Reaction gave an oil which has failed to crystallize and has not been purified or characterized further.

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 1-Methylhexahydro-1H-azepin-4-yl Ester Methoiodide (29). Prepared from **26** (2.2 g, 7.93 mmol) by the same method as **6** to give 2.9 g (87%) of **29**. ^{1}H-NMR (DMSO-d_6) δ 7.33 (s, 5H, aromatic), 5.15 (m, 1H, OC$\underline{H}$), 4.2-3.4 (m, 7H, C$\underline{H}C\underline{H}_2OH$, $C\underline{H}_2NC\underline{H}_2$), 3.32 (s, 3H, N$C\underline{H}_3$), 3.19 (s, 3H, N$C\underline{H}_3$), 1.8-2.5(br m, 6H, ring $C\underline{H}_2$).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 1-Methylhexahydro-1H-azepin-4-yl Ester Methochloride (SR 4972). Prepared from **29** (2.4 g, 5.7 mmol) by the same method as **SR 4950** to give 1.7 g (90%) of **SR 4972**, mp 158-160 °C. ^{1}H-NMR ($CDCl_3$-CD_3OD) δ 7.33 (s, 5H, aromatic), 5.0 (m, 2H, C$\underline{H}$O, O$\underline{H}$), 4.1-3.4 (m, 3H, C$\underline{H}C\underline{H}_2OH$), 3.3 (m, 4H, $C\underline{H}_2N$), 3.29 (s, 3H, N$C\underline{H}_3$), 3.04 (s, 3H, N$C\underline{H}_3$), 1.5-2.4 (br d, 6H, ring $C\underline{H}_2$). Anal calcd for

$C_{17}H_{26}ClNO_3$: C, 62.25; H, 7.99; N, 4.27; Cl, 10.81. Found: C, 60.44; H, 7.93 N, 4.07; Cl, 11.20.

S-(-)-1-Methyl-2-(chloromethyl)pyrrolidine Hydrochloride. To 24 g (0.208 mol) of S-(-)-1-Methyl-2-(hydroxymethyl)pyrrolidine in 100 mL of $CHCl_3$ (EtOH free) at 0 °C was added 19 mL (0.26 mol) of thionyl chloride in 60 mL of $CHCl_3$ over 20 min. The resulting brown solution was stirred at RT for 45 min, then heated at reflux for 30 min. The now purple solution was cooled and evaporated to dryness and the residue taken up in abs EtOH and filtered. Diethyl ether was added until the solution became cloudy. then chilled and filtered to give 22 g (62%) of S-(-)-1-methyl-2-(chloromethyl)pyrrolidine hydrochloride, mp 148-153 °C ^{1}H-NMR ($CDCl_3$) δ 4.5-3.5 (m, 4H, $ClCH_2$, CH_2N), 3.04 (m, 1H, CHN), 3.03 (d, 3H, NCH_3), 2.4-1.9 (m, 6H, ring CH_2s).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, S-(-)-1-Methylpyrrolidin-2-yl-methyl Ester (31) and S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, S-(-)-1-Methylpiperidin-3-yl Ester (32). Prepared from S-(-)-tropic acid (0.33 g, 2.00 mmol) and 0.35 g (2.06 mmol) of S-(-)-1-methyl-2-(chloroethyl)pyrrolidine hydrochloride by the same method as **5** to give 0.5 g (95%) of a 9:1 mixture of **31** and **32** as an oil. ^{1}H-NMR ($CDCl_3$) δ 7.30 (s, 5H, aromatic), 4.6-3.7 (m, 7H, $CHCH_2OH$, CO_2CH_2 [pyrrolidine], CO_2CH [piperidine]), 3.3-1.5 (m, ring CH_2s)2.19 (s, **32**-NCH_3), 2.28 (s, **31**-NCH_3).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, S-(-)-1-Methylpyrrolidin-2-yl-methyl Ester Methoiodide (33) and S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, S-(-)-1-Methylpiperidin-3-yl Ester Methoiodide (35). Prepared from the mixture of **31** and **32** (0.5 g, 1.9 mmol) by the same method as **6** to give 0.8 g (100%) of an oil consisting of a mixture of **33** and **35**. ^{1}H-NMR (CD_3OD) δ 7.33 (s, 5H, aromatic), 4.3-4.5 (m, 3H, $CHCH_2OH$), 5.2 (m, 1H, CO_2CH [piperidine]), 4.53 d, 2H, CO_2CH_2 [pyrrolidine]), 3.17 (s, NCH_3 [pyrrolidine]), 3.00 (s, NCH_3 [pyrrolidine]), 3.22 (s, NCH_3 [piperidine]), 2.92 (s, NCH_3 [piperidine]), 2.7-1.8 (m, ring CH_2s).

S-(-)-α-(t-Butyldimethylsilyloxymethyl)benzeneacetyl Chloride (38). In a flask under argon, 0.5 g (3.00 mmol) of S-(-)-tropic acid was combined with 0.96 g (6.37 mmol) of *t*-butyldimethylsilane and 0.87 g (12.7 mmol) of imidazole in 3 mL of DMF and stirred at RT for 18 h. The mixture was poured into 20 mL of H_2O and extracted with ether. The ether was washed with saturated NaCl solution, dried over $MgSO_4$, filtered and evaporated to give 1.15 g of an oil.

This was taken up in 5 mL of CH_2Cl_2 and 1 drop of DMF, followed by the addition of 286 µL (3.35 mmol) of oxalyl chloride at 0 °C, stirred at 0 °C for 1.5 h, then at RT for 0.5 h. The solution was evaporated to yield 1.2 g of **38** as a syrup which was not purified further. ^{1}H-NMR ($CDCl_3$) δ 7.38 (s, 5H, aromatic), 4.3-3.7 (m, 3H, C<u>H</u>C<u>H</u>$_2$), 0.84 (s, 9H, t-butyl), 0.02 (s, 3H, CH_3), 0.01 (s, 3H, CH_3).

S-(-)-α-(t-Butyldimethylsilyloxymethyl)benzeneacetic Acid, S-(-)1-Methylpyrrolidin-2-ylmethyl Ester (39). To 0.34 g (2.91 mmol) of S-(-)-1-methyl-2-pyrrolidinemethanol and 295 µL (2.92 mmol) of triethylamine in 5 mL of CH_2Cl_2 at 0 °C was added 0.872 g (2.91 mmol) of **38** in 2 mL of CH_2Cl_2. The solution was stirred at 0 °C for 1 h, then washed with satd $NaHCO_3$ solution. The organic fraction was dried over $MgSO_4$ filtered and evaporated to dryness. The residue was purified by flash chromatography to give 0.21 g (19%) of **39**. ^{1}H-NMR ($CDCl_3$) δ 7.42 (s, 5H, aromatic), 4.5-3.7 (m, 3H, C<u>H</u>C<u>H</u>$_2$, O<u>CH</u>$_2$), 2.43 (s, 3H, NCH_3), 2.7-1.5 (m, 6H, ring CH_2), 0.98 (s, 9H, *t*-butyl), 0.15 (s, 3H, CH_3), 0.13 (s, 3H, CH_3).

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, S-(-)-1-Methylpyrrolidin-2-ylmethyl Ester (31) and S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, 1-Methylpiperidin-3-yl Ester (41). A solution of 0.25 g (0.66 mmol) of **38** in 5 mL of THF was treated with 0.6 g (1.98 mmol) of tetrabutylammonium fluoride, stirred for 1 h, then evaporated to dryness. The residue was partitioned between H_2O (20 mL) and ether (20 mL), and the ether layer washed with satd NaCl solution, dried over $MgSO_4$, filtered and evaporated to give 0.15 g (86%) of an oil consisting of a mixture of **31** and **41**.

S-(-)-α-(Hydroxymethyl)benzeneacetic Acid, S-(-)-1-Methylpyrrolidin-2-ylmethyl Ester (31). In a small flask, **39** in 3 mL of AcOH/H_2O/THF (3/1/1/) was stirred at RT for 5 days. The solution was evaporated to dryness in vacuo to give 0.11 g (90%) of **31** as a syrup.

4'-Chlorobenzeneacetic acid, Methyl Ester (44). To 34 g (0.200 mol) of 4'-chlorobenzeneacetic acid (**43**) in 120 mL of MeOH at 0 °C was added 80 mL of MeOH saturated with HCl gas. The solution was stirred for 20 h, then evaporated to an oil. This was taken up in 150 mL of CH_2Cl_2, washed with satd $NaHCO_3$ and satd NaCl solution, dried over $MgSO_4$, filtered and evaporated to give 37 g (100%) of **44**. ^{1}H-NMR ($CDCl_3$) δ 7.27 (q 4H, aromatic), 4.3-3.7 (m, 2H, C<u>H</u>$_2$), 3.71 (s, 3H, OCH_3).

(±)-4-Chlorotropic acid, Methyl Ester (45). Into a flask, flame dried under argon, was placed a slurry of 37 g (0.20 mol) of 44 and 750 g of paraformaldehyde in 120 mL of dry DMF, followed by the addition of 0.650 g (12 mmol) of sodium methoxide in one portion. This was stirred for 1.5 h, then poured into 300 mL of H_2O and extracted with ether (3 x 250 mL). The ether fraction was washed with satd NaCl solution, dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography eluting with 1%MeOH in $CHCl_3$ to give 21 g (49%) of **45**. ^{1}H-NMR ($CDCl_3$) δ 7.27 (q 4H, aromatic), 4.3-3.7 (m, 3H, C<u>H</u>C<u>H</u>$_2$OH), 3.71 (s, 3H, OCH_3).

(±)-4-Chlorotropic Acid (46). To 22 g of **45** in 10 mL of THF was added 18 mL (108 mmol) of 6 N NaOH and the mixture stirred for 18 h. The THF was removed by evaporation and the residue taken up in H_2O, followed by the addition of 6N HCl until no more solid precipitated. The solid was collected by filtration and washed with water, then dried in vacuo to give 20 g (98%) of **46**. ^{1}H-NMR (DMSO-d_6) δ 7.19 (s 4H, aromatic), 4.1-3.5 (m, 3H, C<u>H</u>C<u>H</u>$_2$), 6.90 (br, 2H, CO_2<u>H</u>, O<u>H</u>).

(-)-4-Chlorotropic Acid (47). Prepared from **46** (10 g, 50 mmol) and quinine hydrate (17.5 g, 51 mmol) by the same method as **1** to give 3.5 g (13%) of **47•quinine salt**, mp 190-192 °C. This was stirred in 20 mL of 1N H_2SO_4 for 0.5 h, followed by the addition of 100 mL of EtOAc and 25 mL of satd NaCl solution. The layers were separated and the aqueous layer extracted with EtOAc. The combined organic fraction was washed with satd NaCl solution, dried over $MgSO_4$, filtered and evaporated to give 1.3 g (13%) of **47**. $[\alpha]_D$ = -58 (2.5% in 95%EtOH).

S-(-)-4'-Chloro-α-(hydroxymethyl)benzeneacetic Acid, 2-(*N,N*-Diethylamino)-ethyl Ester (48). Into a flask was placed 3.4 g (17.0 mmol) of (-)-4-chlorotropic acid (**47**) and 3.4 g (30.0 mmol) of powdered K_2CO_3 in 150 mL of DMF. This was stirred at RT for 6 h, followed by the addition of 2-*N,N*-diethylaminoethyl chloride hydrochloride. The mixture was stirred at room temp for 3 days. This was poured into 500 mL of water and extracted with Et_2O (3 x 200 mL). The ether layer was washed with satd NaCl solution (550 mL), dried over $MgSO_4$, filtered and evaporated to give 3.0 g (58.9%) of an oil. The aqueous layer was acidified with HCl to pH 2-3 and extracted with $CHCl_3$ (3 x 200 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated under high vac to give 1.2 g of recovered starting material. This was treated as above with 2X the ratio of DMF. Workup as above afforded an additional 1.2 g of an oil (total 4.2 g). The oil was chromatographed on silica gel with 1-4% [MeOH/NH4OH(95/5)] in

CH_2Cl_2 to give 3.6 g (71%) of **48** as an oil. $[\alpha]_D$ = -15.9 ° (2.69% in 95% EtOH) 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.29 (s, 4H, aromatic), 4.6-3.7 (m, 6H, $CO_2C\underline{H}_2$, $C\underline{H}C\underline{H}_2O\underline{H}$), 2.69 (t, 2H, $C\underline{H}_2N$, J=5.7 Hz), 2.57 (q, 4H, $N[C\underline{H}_2Me]_2$, J=7.0 Hz), 1.02 (t, 6H, $N[CH_2C\underline{H}_3]_2$, J=7.0 Hz).

S-(-)-4'-Chloro-α-(hydroxymethyl)benzeneacetic Acid, 2-(*N,N*-Diethylamino)-ethyl Ester Methoiodide (49). Into a flask was placed 3.0 g (10 mmol) of **48** in 10 mL of CH_3CN. This was treated with 3 mL of CH_3I and the yellow solution stirred for 7 days. An additional 3 mL of CH_3I was added and the mixture stirred for 3 days and evaporated. The residue was allowed to stand in 10 mL of MEK and a trace of Et_2O at -5 °C for 5 days. The solid was filtered to give 1.9 g (43%) of **49**. 90 MHz ^{1}H-NMR (CD_3CN) δ 7.35 (s, 4H, aromatic), 4.45 (unresolved t, 2H, $CO_2C\underline{H}_2$), 5.1-3.4 (m, 4H, $C\underline{H}C\underline{H}_2O\underline{H}$), 3.42 (m, 2H, $C\underline{H}_2N$), 3.38 (q, 4H, $N[C\underline{H}_2Me]_2$, J=7.2 Hz), 2.92 (s, 3H, $NC\underline{H}_3$), 1.21 (t, 6H, $N[CH_2C\underline{H}_3]_2$, J=7.2 Hz).

S-(-)-4'-Chloro-α-(hydroxymethyl)benzeneacetic Acid, 2-(*N,N*-Diethylamino)-ethyl Ester Methochloride (SR 4973). Prepared from **49** (1.9 g, 4.3 mmol) in the same manner as **SR 4950** to give 1.5 g of a colorless oil. This was taken up in 1 mL of iPrOH and 10 mL of MEK and chilled at -10 °C for 7 days with the formation of crystals. Stirring caused more crystals to form and the solid was collected by filtration. The solid softened very quickly before the filtration was complete. This residue was taken up in MeOH and evaporated under high vac to give **SR 4973** as a solid. 90 MHz ^{1}H-NMR (CD_3CN) δ 7.35 (s, 4H, aromatic), 5.25 (m, 1H, OH), 4.50 (unresolved dd, 2H, $CO_2C\underline{H}_2$), 4.2-3.55 (m, 5H, $C\underline{H}_2N$, $C\underline{H}C\underline{H}_2O\underline{H}$), 3.39 (q, 4H, $N[C\underline{H}_2Me]_2$, J=7.0 Hz), 3.00 (s, 3H, $NC\underline{H}_3$), 1.23 (t, 6H, $N[CH_2C\underline{H}_3]_2$, J=7.0 Hz). Anal. Calcd for $C_{16}H_{25}Cl_2NO_3$: Theory: C, 54.86; H, 7.19; N, 4.00; Cl, 20.24. Found: C, 54.65; H, 7.44; N, 4.17; Cl, 20.36.

S-(-)-4'-Chloro-α-(hydroxymethyl)benzeneacetic Acid, 2-(*N,N*-Diethylamino)-ethyl Ester Ethoiodide (50). Prepared from **48** (0.60 g, 2 mmol) and ethyl iodide (2 mL) in the same manner as **6** to give 0.71 g (78%) of a yellow oil. This was crystallized from iPrOH/MEK to give 0.40 g (44%) of **50** as a light yellow solid. $[\alpha]_D$= -8.84 ° (2.55% in 95% EtOH) 90 MHz ^{1}H-NMR (CD_3CN) δ 7.34 (s, 4H, aromatic), 4.42 (unresolved t, 2H, $CO_2C\underline{H}_2$), 4.1-3.7 (m, 4H, $C\underline{H}C\underline{H}_2O\underline{H}$), 3.49 (t, 2H, $C\underline{H}_2N$), 3.24 (q, 6H, $N[C\underline{H}_2Me]_3$), 1.12 (t, 9H, $N[CH_2C\underline{H}_3]_3$).

S-(-)-4'-Chloro-α-(hydroxymethyl)benzeneacetic Acid, 2-(*N,N*-Diethylamino)-ethyl Ester Ethochloride (SR 4975). Prepared from **50** (0.350 g, 0.768 mmol) in the same

manner as **SR 4950**. Lyophilization gave a glass. This was slowly recrystallized from iPrOH/MEK/Et_2O to give 60 mg (20%) of **SR 4975** as hygroscopic crystals, mp 65-75 °C Evaporation of the mother liquor under high vac gave an oil which was 99% pure by RP-HPLC (phenyl column). $[\alpha]_D$= -11.6 ° (2.09% in 95% EtOH) 90 MHz ^{1}H-NMR (CD_3CN) δ 7.34 (s, 4H, aromatic), 4.42 (unresolved t, 2H, $CO_2C\underline{H}_2$), 4.1-3.7 (m, 4H, $C\underline{H}C\underline{H}_2O\underline{H}$), 3.45 (t, 2H, $C\underline{H}_2N$), 3.24 (q, 6H, $N[C\underline{H}_2Me]_3$), 1.12 (t, 9H, $N[CH_2C\underline{H}_3]_3$). Anal. Calcd for $C_{17}H_{27}Cl_2NO_3 \cdot 1/3H_2O$: Theory: C, 55.15; H, 7.53; N, 3.78; Cl, 19.15. Found: C, 55.40; H, 7.53; N, 3.72; Cl, 18.76.

S-(-)-4'-Chloro-α-(hydroxymethyl)benzeneacetic Acid, 2-(*N-Iso*-propyl-*N*-methylamino)ethyl Ester (51). Prepared from (-)-4-chlorotropic acid (**47**) (1.2 g, 7.0 mmol) and 2-(*N-iso*-propyl-*N*-methylamino)ethyl chloride hydrochloride (**11**) (1.2 g, 7.0 mmol) in the same manner as **5** to give 1.5 g (83%) of a dark oil. This was chromatographed on silica gel eluting with 0.1 - 5% [MeOH/NH_4OH(95/5)] in CH_2Cl_2 to give 1.1 g (61%) of **51** as a clear oil. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.28 (s, 4H, aromatic), 4.5-3.7 (m, 6H, $CO_2C\underline{H}_2$, $C\underline{H}C\underline{H}_2O\underline{H}$), 2.90 (q, 1H, $NC\underline{H}Me_2$), 2.66 (t, 2H, $C\underline{H}_2N$), 2.21 (s, 3H, $NC\underline{H}_3$), 1.01 (d, 6H, $NCH[C\underline{H}_3]_2$).

S-(-)-4'-Chloro-α-(hydroxymethyl)benzeneacetic Acid, 2-(*N-Iso*-propyl-*N*-methylamino)ethyl Ester Methoiodide (52). Prepared from **51** (1.1 g, 3.67 mmol) and methyl iodide (2 mL) in the same manner as **6** to give 1.4 g (89%) of an oil. This was dissolved in 1 mL of iPrOH and 40 mL of MEK and chilled overnight at -10 °C. A light yellow solid was filtered to give 0.64 g (40%) of **52**, mp 131-133 °C. $[\alpha]_D$= -8.3 ° (1.20% in 95% EtOH) 90 MHz ^{1}H-NMR (CD_3CN) δ 7.32 (s, 4H, aromatic), 4.45 (unresolved t, 2H, $CO_2C\underline{H}_2$), 4.1-3.6 (m, 5H, $NC\underline{H}Me_2$, $C\underline{H}C\underline{H}_2O\underline{H}$), 3.55 (t, 2H, $C\underline{H}_2N$), 2.89 (s, 6H, $N[C\underline{H}_3]_2$), 1.24 (d, 6H, $NCH[C\underline{H}_3]_2$).

S-(-)-4'-Chloro-α-(hydroxymethyl)benzeneacetic Acid, 2-(*N-Iso*-propyl-*N*-methylamino)ethyl Ester Methochloride (SR 4976). Prepared from **52** (0.64 g, 1.44 mmol) in the same manner as **SR 4950** to give a clear syrup after lyophilization. This was crystallized from iPrOH/MEK to give 0.45 g (91%) of **SR 4976**. $[\alpha]_D$= -10.5 ° (1.12% in 95% EtOH) 400 MHz ^{1}H-NMR (CD_3CN) δ 7.35 (s, 4H, aromatic), 4.48 (m, 2H, $CO_2C\underline{H}_2$), 4.45 (t, 1H, $O\underline{H}$), 4.00 (ddd, 1H, $CHC\underline{H}_2OH$), 3.78 (ddd, 1H, $CHC\underline{H}_2OH$), 3.89 (dd, 1H, $C\underline{H}$), 3.75 (q, 1H, $NC\underline{H}Me_2$,), 3.61 (ddd x ddd, 2H, $C\underline{H}_2N$), 2.05 (s, 6H, $N[C\underline{H}_3]_2$), 1.30 (d, 6H, $NCH[C\underline{H}_3]_2$). Anal. Calcd for $C_{16}H_{25}Cl_2NO_3$: Theory: C, 54.86; H, 7.19; N, 4.00; Cl, 20.24. Found: C, 54.68; H, 7.19; N, 3.97; Cl, 19.83.

S-(-)-4'-Chloro-α-(hydroxymethyl)benzeneacetic Acid, 2-(*N,N*-Di-*iso*-propylamino)ethyl Ester (53). Prepared from (-)-4-chlorotropic acid (**47**) (1.0 g, 5.0 mmol) and 2-*N,N*-di-*iso*-propylaminoethyl chloride hydrochloride (1.2 g, 6.0 mmol) in the same manner as **5** to give 1.2 g (73%) of an oil. This was chromatographed twice on silica gel eluting with 0.1 - 5% [MeOH/NH_4OH(95/5)] in CH_2Cl_2 to give 0.20 g (12%) of **53** as a clear syrup. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.29 (s, 4H, aromatic), 4.3-3.6 (m, 6H, $CO_2C\underline{H}_2$, $C\underline{H}C\underline{H}_2O\underline{H}$), 3.03 (q, 1H, $NC\underline{H}Me_2$), 2.67 (t, 2H, $C\underline{H}_2N$), 1.00 (d, 12H, $N[CH[C\underline{H}_3]_2]_2$).

S-(-)-4'-Chloro-α-(hydroxymethyl)benzeneacetic Acid, 2-(*N,N*-Di-*iso*-propylamino)ethyl Ester Methoiodide (54). Prepared from **53** (0.195 g, 0.60 mmol) and methyl iodide (3 mL) in the same manner as **6** to give 0.28 g (100%) of a solid. This was dissolved in 1 mL of iPrOH and 20 mL of MEK, Et_2O was added to the cloud point, and the mixture chilled for 3 days at -10 °C to give 0.12 g (42%) of **54** in two crops, mp 133-136 °C. $[\alpha]_D$= -10.5 ° (0.32% in 95% EtOH) 90 MHz ^{1}H-NMR (CD_3CN) δ 7.34 (s, 4H, aromatic), 4.40 (t, 2H, $CO_2C\underline{H}_2$), 4.1-3.5 (m, 5H, $NC\underline{H}Me_2$, $C\underline{H}C\underline{H}_2O\underline{H}$), 3.46 (t, 2H, $C\underline{H}_2N$), 2.74 (s, 3H, $NC\underline{H}_3$), 1.30 (d, 12H, $N[CH[C\underline{H}_3]_2]_2$).

S-(-)-4'-Chloro-α-(hydroxymethyl)benzeneacetic Acid, 2-(*N,N*-Di-*iso*-propylamino)ethyl Ester Methochloride (SR 4977). Prepared from **54** (0.110 g, 0.23 mmol) in the same manner as **SR 4950** to give 95 mg (86%) of an oil after lyophilization. A solid melting below room temp was crystallized from (1/20/trace) iPrOH/MEK/Et_2O at -10 °C to give 50 mg (56%) of **SR 4977**. $[\alpha]_D$= -5 ° (0.35% in 95% EtOH) 90 MHz ^{1}H-NMR (CD_3CN) δ 7.33 (s, 4H, aromatic), 4.45 (t, 2H, $CO_2C\underline{H}_2$), 4.1-3.7 (m, 5H, $CHC\underline{H}_2O\underline{H}$, $N[C\underline{H}Me_2]_2$), 3.82 (s, 3H, $NC\underline{H}_3$), 3.52 (t, 2H, $C\underline{H}_2N$), 1.32 (d, 12H, $N[CH[C\underline{H}_3]_2]_2$).

α-(Hydroxymethyl)-4'-methoxybenzeneacetic Acid, 2-(*N,N*-Diethylamino)ethyl Ester (60). Prepared from 4-methoxytropic acid (**58**)[16] (4.0 g, 20.4 mmol) and 2-*N,N*-diethylaminoethyl chloride hydrochloride (3.8 g, 22 mmol) in the same manner as **5** to give 4.0 g (66%) of an oil. This was chromatographed on silica gel eluting with 10-15% [MeOH/NH_3 (95/5)] in CH_2Cl_2 to give 1.2 g (20%) of **60** as an oil. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.26 (m, 2H, aromatic H-2, H-6), 6.87 (m, 2H, aromatic H-3, H-5), 4.19 (t, 2H, $CO_2C\underline{H}_2$), 4.1-3.6 (m, 4H, $C\underline{H}C\underline{H}_2O\underline{H}$), 3.75 (s, 3H, $OC\underline{H}_3$), 2.62 (t, 2H, $C\underline{H}_2N$, J=5.7 Hz), 2.49 (q, 4H, $N[C\underline{H}_2Me]_2$), 0.953 (t, 6H, $N[CH_2C\underline{H}_3]_2$, J=7.0 Hz).

α-(Hydroxymethyl)-4'-methoxybenzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester Methoiodide (61). Prepared from **60** (0.60 g, 2.03 mmol) and methyl iodide (2.0 mL, 32 mmol) in the same manner as **6** to give 0.78 g (88%) of **61**, mp 113-116 °C. 90 MHz ^{1}H-NMR (CD_3CN) δ 7.23 (d x t, 2H, aromatic H-2, H-6), 6.89 (m, 2H, aromatic H-3, H-5), 4.42 (m, 2H, $CO_2C\underline{H}_2$), 4.10-3.60 (m, 4H, $C\underline{H}C\underline{H}_2O\underline{H}$), 3.76 (s, 3H, $OC\underline{H}_3$), 3.45 (m, 2H, $C\underline{H}_2N$), 3.22 (q, 4H, $N[C\underline{H}_2Me]_2$, J=7.3 Hz), 2.34 (s, 3H, $NC\underline{H}_3$), 1.19 (t, 6H, $N[CH_2C\underline{H}_3]_2$, J=7.3 Hz).

α-(Hydroxymethyl)-4'-methoxybenzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester Methochloride (SR 4978). Prepared from **61** (0.78 g, 1.77 mmol) in the same manner as **SR 4950** to give 0.61 g (99 %) of **SR 4978.** 90 MHz ^{1}H-NMR (CD_3CN) δ 7.25-6.85 (m, 4H, aromatic H-2, H-3, H-5 and H-6), 4.48 (m, 2H, $CO_2C\underline{H}_2$), 4.05-3.60 (m, 4H, $C\underline{H}C\underline{H}_2O\underline{H}$), 3.75 (s, 3H, $OC\underline{H}_3$), 3.60 (m, 2H, $C\underline{H}_2N$), 3.34 (q, 4H, $N[C\underline{H}_2Me]_2$, J=7.0 Hz), 2.96 (s, 3H, $NC\underline{H}_3$), 1.22 (t, 6H, $N[CH_2C\underline{H}_3]_2$, J=7.0 Hz).

α-(Hydroxymethyl)-4'-methoxybenzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester Ethoiodide (62). Prepared from **60** (0.60 g, 2.03 mmol) and ethyl iodide (2.0 mL, 25 mmol) in the same manner as **6** to give 0.74 g (81 %) of **62**, mp 94-96 °C. 90 MHz ^{1}H-NMR (CD_3CN) δ 7.23 (m, 2H, aromatic H-2, H-6), 6.89 (m, 2H, aromatic H-3, H-5), 4.38 (m, 2H, $CO_2C\underline{H}_2$), 4.20-3.60 (m, 4H, $C\underline{H}C\underline{H}_2O\underline{H}$), 3.76 (s, 3H, $OC\underline{H}_3$), 3.40 (m, 2H, $C\underline{H}_2N$), 3.19 (q, 6H, $N[C\underline{H}_2Me]_3$, J=7.0 Hz), 1.15 (t, 9H, $N[CH_2C\underline{H}_3]_3$, J=7.0 Hz).

α-(Hydroxymethyl)-4'-methoxybenzeneacetic Acid, 2-(*N*,*N*-Diethylamino)ethyl Ester Ethochloride (SR 4979). Prepared from **62** (0.74 g, 1.64 mmol) in the same manner as **SR 4950** to give 0.60 g (100 %) of **SR 4979.** 90 MHz ^{1}H-NMR (CD_3CN) δ 7.25 (m, 2H, aromatic H-2, H-6), 6.87 (m, 2H, aromatic H-3, H-5), 4.43 (m, 2H, $CO_2C\underline{H}_2$), 4.10-3.60 (m, 4H, $C\underline{H}C\underline{H}_2O\underline{H}$), 3.75 (s, 3H, $OC\underline{H}_3$), 3.50 (m, 2H, $C\underline{H}_2N$), 3.27 (q, 6H, $N[C\underline{H}_2Me]_3$, J=7.4 Hz), 1.18 (t, 9H, $N[CH_2C\underline{H}_3]_3$, J=7.4 Hz).

5-Bromovaleraldehyde Ethylene Acetal. 5-Bromovaleraldehyde (23 g, 139 mmol) was combined with 12.5 g (402 mmol) of ethylene glycol and 3 crystals of *p*-toluenesulfonic acid in 400 mL of toluene and heated at reflux in a Dean-Stark trap for 10 h. The solvent was reduced to ~20 mL, diluted with 200 mL of CH_2Cl_2, washed with 200 mL of satd $NaHCO_3$ and 200 mL of NaCl solution, dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography to give 5.2 g (18%) of 5-bromovaleraldehyde ethylene acetal. Additional

fractions were obtained, of lower purity (6.2 g, 98% purity; 5.0 g, 89% purity). ^{1}H-NMR ($CDCl_3$) δ 4.86 (t, 1H, C<u>H</u>), 4.0-3.8 (m, 4H, OC<u>H</u>$_2$), 3.41 (t, 2H, C<u>H</u>$_2$Br), 1.4 -2.1 (m, 6H, C<u>H</u>$_2$).

Methyl 7-Ethylenedioxy-2-phenylheptanoate (66). A trace of Na was added to ~15 mL of liquid ammonia, followed by a crystal of ferric nitrate. This was stirred until the blue color changed to a clear solution with a dark solid. To this mixture was added 0.13 g (5.62 mmol) of Na and stirring continued until the blue color became a black precipitate. To this was slowly added 0.90 g (6.0 mmol) of benzeneacetic acid, methyl ester (**65**), followed by stirring at -33 °C for 0.5 h. To this brown mixture was added 1.0 g (4,78 mmol) of 5-bromovaleraldehyde ethylene acetal in 5 mL of ether with stirring continued at -33 °C for 2 h. Ammonium chloride (0.30 g, 5.6 mmol) was added and the ammonia allowed to evaporate off. The residue was taken up in ether, washed with satd NaCl solution, dried over $MgSO_4$, filtered and evaporated to give an oil. This was purified by flash chromatography eluting with CH_2Cl_2 to give 1.2 g (86%) of **66**. R_f 0.3 (CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) δ 7.28 (s, 5H, aromatic), 4.81 (t, 1H, OC<u>H</u>O), 4.0-3.7 (m, 4H, OC<u>H</u>$_2$), 3.64 (s, 3H, OC<u>H</u>$_3$), 3.54 (t, 1H, C<u>H</u>), 1.1-2.4 (m, 8H, C<u>H</u>$_2$).

Methyl 7-Oxo-2-phenylheptanoate (67). To a mixture of 8 g silica gel and 0.8 mL of 10% oxalic acid in 5 mL of CH_2Cl_2 was added 0.8 g (2.87 mmol) of **66**. The mixture was stirred at RT for 5 days, followed by the addition of 0.075 g (0.9 mmol) of powdered $NaHCO_3$ and stirring for an additional 0.5 h. To this mixture was added ~2 g of $MgSO_4$, and the entire mixture added to a flash chromatography column and eluted with CH_2Cl_2/cyclohexane/MEK (50/49.5/0.5) to give 0.43 g (66%) of **67** and 0.20 g of recovered starting material. ^{1}H-NMR ($CDCl_3$) δ 9.72 (t, 1H, aldehyde H), 7.28 (s, 5H, aromatic), 3.64 (s, 3H, OC<u>H</u>$_3$), 3.54 (t, 1H, C<u>H</u>CO$_2$Me), 2.41 (d of t, 2H, CH_2CHO), 1.8-0.9 (m, 6H, C<u>H</u>$_2$).

6-Ethylenedioxy-2-phenylhexyl Cyanide (71). Into a flask equipped with a dry ice condenser was placed 0.47 g (12.0 mmol) of sodium amide in 30 mL of liquid NH_3, followed by the slow addition of 1.7 g (14.5 mmol) of benzyl cyanide (**70**) in 5 mL of Et_2O. After stirring for 0.5 h at -33 °C (refluxing NH_3), 2.10 g (10 mmol) of 5-bromovaleraldehyde ethylene acetal in 5 mL of Et_2O was slowly added to the yellow-green solution. This was stirred at -33 °C for 2 h, during which time the solution became dark brown, followed by the addition of 0.530 g of NH_4Cl. The NH_3 was allowed to evaporate, Et_2O was added and the mixture washed with satd NaCl soln (100 mL). The ether layer was dried over $MgSO_4$, filtered and evaporated to dryness to give 3.1 g. This was purified on a flash column eluting with CH_2Cl_2 to give 2.1 g (85%) of **71**.

90 MHz ^{1}H-NMR ($CDCl_3$) δ 7.34 (s, 5H, aromatic), 4.83 (t, 1H, $CH_2C\underline{H}O_2$), 4.1-3.7 (m, 4H, $OC\underline{H}_2C\underline{H}_2O$), 3.78 (t, 1H, C<u>H</u>CN), 2.1-1.3 (m, 8H, $[C\underline{H}_2]_4$).

6-Oxo-2-phenylhexyl Cyanide (72). To a flask containing 24 g of silica gel in 15 mL of CH_2Cl_2 and 2.4 mL of 15% H_2SO_4 was added 2.1 g (8.5 mmol) of **71** and the mixture was stirred for 6 days. $NaHCO_3$ (0.65 g, 7.7 mmol) was added to neutralize the H_2SO_4, followed by the addition of ~6 g of $MgSO_4$. This mixture was added to the top of a flash column and eluted with 0.5% MEK in (1/1) cyclohexane/CH_2Cl_2 to give 0.8 g of recovered starting material and 0.99 g (57%) of **71**. 90 MHz ^{1}H-NMR ($CDCl_3$) δ 9.75 (t, 1H, $CH_2C\underline{H}O$, J=1.2 Hz), 7.34 (s, 5H, aromatic), 3.79 (t, 1H, $CH_2C\underline{H}CN$, J=7.0 Hz), 2.45 (t, 2H, $C\underline{H}_2CHCN$, J=6.0 Hz), 2.1-1.3 (m, 6H, $[C\underline{H}_2]_3$).

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